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Novel pharmacological targets in drug development for the treatment of anxiety and anxiety-related disorders

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ABSTRACT

Current medication for anxiety disorders is suboptimal in terms of efficiency and tolerability, highlighting the need for improved drug treatments. In this review an overview of drugs being studied in different phases of clinical trials for their potential in the treatment of fear-, anxiety- and trauma-related disorders is presented. One strategy followed in drug development is refining and improving compounds interacting with existing anxiolytic drug targets, such as serotonergic and prototypical GABAergic benzodiazepines. A more innovative approach involves the search for compounds with novel mechanisms of anxiolytic action using the growing knowledge base concerning the relevant neurocircuitries and neurobiological mechanisms underlying pathological fear and anxiety. The target systems evaluated in clinical trials include glutamate, endocannabinoid and neuropeptide systems, as well as ion channels and targets derived from phytochemicals. Examples of promising novel candidates currently in clinical development for generalised anxiety disorder, social anxiety disorder, panic disorder, obsessive compulsive disorder or post-traumatic stress disorder include ketamine, riluzole, xenon with one common pharmacological action of modulation of glutamatergic neurotransmission, as well as the neurosteroid aloradine. Finally, compounds such as D-cycloserine, MDMA, L-DOPA and cannabinoids have shown efficacy in enhancing fear-extinction learning in humans. They are thus investigated in clinical trials as an augmentative strategy for speeding up and enhancing the long-term effectiveness of exposure-based psychotherapy, which could render chronic anxiolytic drug treatment dispensable for many patients. These efforts are indicative of a rekindled interest and renewed optimism in the anxiety drug discovery field, after decades of relative stagnation.

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Abbreviations: 2-AG, 2-arachidonoylglycerol; 5-HT, serotonin, 5-hydroxytryptamine; AEA, anandamide; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; BDZ, benzodiazepine; CB_1/CB_2, cannabinoid receptor type 1 or 2; CBD, cannabidiol; CBT, cognitive behavioural therapy; CNS, central nervous system; COX-2, cyclooxygenase-2; CRH, corticotropin releasing hormone; D_{1-5}, dopamine receptor subtypes 1–5; DREADDs, Designer Receptors Exclusively Activated by Designer Drugs; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, version 5; EBT, exposure-based therapy; eCB, endocannabinoid; EMA, European Medicines Agency; ER, extended release; FAAH, fatty acid amide hydrolase; FDA, Food and Drug Administration of the United States; GABA, γ-aminobutyric acid; GAD, generalised anxiety disorder; ICD 10/11, International Statistical Classification of Diseases and Related Health Problems, version 10/11; IL, infralimbic cortex; L-DOPA, L-3,4-dihydroxyphenylalanine; LSD, lysergic acid diethylamide; MAG-L, monoacylglycerol lipase; MAPK, mitogen-activated protein kinase; mGluR, metabotropic glutamate receptor; mPFC, medial prefrontal cortex; mTOR, mammalian target of rapamycin; NCT, National Clinical Trial; NMDA, *N*-methyl-D-aspartate; NPS, neuropeptide S; NPY, neuropeptide Y; OCD, obsessive compulsive disorder; OXT, oxytocin; PAM, positive allosteric modulator; PD, panic disorder; PFC, prefrontal cortex; PTSD, post-traumatic stress disorder; RDoc, Research Domain Criteria; SAD, social anxiety disorder; SNRI, serotonin and noradrenaline re-uptake inhibitor; SSRI, selective serotonin re-uptake inhibitor; THC, tetrahydrocannabinol; V_{1A}/V_{1B}, vasopressin receptor 1A or 1B.

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1. Introduction

Anxiety is an emotional response to potential future threat or danger, eliciting symptoms of negative affective, somatic, behavioural and cognitive components along a continuum based on intensity and duration. While 'normal' anxiety is adaptive to alert and prepare the organism for the potential threat, anxiety is considered pathologic when it becomes maladaptive, permanent and uncontrollable, negatively affecting daily life. Likewise, fear is an instinctual and/or learned response to immanent threat that is also adaptive and critical for survival when short-lived, but can lead to anxiety disorders when aberrant and chronic. Hence, although fear and anxiety are distinct (Perusini & Fanselow, 2015; Parsafar & Davis, 2018), there are clear overlaps, as well as co-occurrence, as anxiety often follows a fearful experience and in turn modulates the fear responses to a threat. Abnormal, maladaptive forms of these emotions are the hallmarks of fear-, anxiety- and trauma-related disorders. A vulnerability towards the development of anxiety disorders (Gottschalk & Domschke, 2018; Otowa et al., 2016) often starts in childhood or adolescence (Kalin, 2017) and becomes chronic, persisting into adulthood (Bandelow & Michaelis, 2015; Craske et al., 2017). In the Western world, the life time prevalence of these disorders is approximately 20–30% in the general population, making them the most frequent neuropsychiatric disorders, with women being significantly more often affected than men (Bandelow & Michaelis, 2015; DALYs and Collaborators, 2018; Remes, Brayne, van der Linde, & Lafortune, 2016; Revicki et al., 2012; Wittchen & Jacobi, 2005). The classification of anxiety disorders has a long history (Crocq, 2015). Based on clinical observation criteria, the current version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) categorises anxiety disorders into generalised anxiety disorder (GAD), phobias, social anxiety disorder (SAD), post-traumatic stress disorder (PTSD), panic disorder (PD) with/without agoraphobia, and obsessive-compulsive disorder (OCD), while PTSD and OCD are listed in separate chapters of the newest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and in the upcoming ICD-11 (Kogan et al., 2016; Reed et al., 2019). Considering that anxiety symptoms are typically core features of all of these disorders and they have in part overlapping neurobiological mechanisms, the drug development for anxiety disorders, PTSD and OCD is discussed jointly in this review and the used term anxiety and related disorders includes all of these disorders.

Anxiety disorders cause great suffering for patients, as well as placing a huge burden on their families and on societal resources, and they contribute to the development of depression, substance abuse, physical illnesses and other adverse outcomes (Kariuki-Nyuthe & Stein, 2015). In 2010, medical health care utilisation, sick leave, early retirement and reduced productivity at work cost approximately €75 billion in Europe (Olesen et al., 2012), underlining the enormous financial burden caused by anxiety disorders. According to the ESEMeD (European Study of the Epidemiology of Mental Disorders) study, only 20% of people diagnosed with an anxiety disorder seek help from health care services, and only a proportion of those receive adequate treatment. Current treatment options are based mainly on psychotherapy, which has proven effective in anxiety disorders, but unfortunately is often not available (e.g. (Carpenter et al., 2018), see also Section 8), and pharmacotherapy (see Table 1). Of those who receive treatment, non-compliance and non- or incomplete response as well as relapse remain substantial issues (Roy-Byrne, 2015; Taylor, Abramowitz, & McKay, 2012). In treatment-resistant patients (Bokma et al., 2019) showing only little or no improvement to pharmaco- and/or psychotherapy, brain stimulation therapies, including electroconvulsive therapy, transcranial magnetic stimulation, vagus nerve stimulation and deep brain stimulation, can be considered (Kar & Sarkar, 2016; Lebois, Seligowski, Wolff, Hill, & Ressler, 2019). Taken together, there is still an urgent need for the development of novel approaches in the treatment of anxiety and related disorders (Griebel & Holmes, 2013).

The aim of this review is to discuss the status of new pharmacological approaches in this field. We start with a brief historical account of anxiolytic drug development and subsequently discuss new targets arising from the current neurobiological understanding of anxiety mechanisms. We will present four current main avenues for the development of novel anti-anxiety drugs: 1. Refining and improving agents acting on existing drug targets (Section 5); 2. Investigating drugs with novel mechanisms of action (Section 6); 3. Investigating phytochemicals (Section 7); and 4. Utilizing the pharmacological augmentation of psychotherapy (Section 8). A comprehensive search of the US National Institutes of Health's clinicaltrials.gov index for ongoing [active, not yet recruiting, recruiting, enrolling by invitation, and recently suspended (as in September 2018 and updated in April 2019)] trials involving pharmacotherapy to treat GAD, SAD, specific phobias, PD, PTSD and OCD was complemented with an open search through the internet using the terms 'novel or new' and 'anxiolytic or treatment anxiety disorders' to find press releases and announcements. Compounds thereby identified were then used as search terms in a PubMed search. We will provide a short synopsis of clinical and preclinical studies, as well as of approved and ongoing clinical trials supporting the efficacy of these potential drugs for the treatment of anxiety- and related disorders.

2. Overview and historical account of current medication options for anxiety and related disorders

Drugs to reduce anxiety have been used for centuries. The first two anxiolytics, whose general use is documented already thousands of years ago, are opium and ethanol. Ethanol continues to be widely used in self-treatment of anxiety. It was not until the more recent past that the first synthetic sedatives/hypnotics like bromides, paraldehyde, chloral hydrate (19th century) and in particular barbiturates (between 1920s and 1950s, diethyl-barbituric acid introduced 1904 for clinical use) were used as treatments to oppose anxiety symptoms. The use of barbiturates for anxiety and sleep disorders declined rapidly after the introduction of meprobamate and, in particular, the safer benzodiazepines (BDZ) (Wick, 2013) in the 50s and 60s of the 20th century. The BDZs were discovered by Leo Sternbach in 1955 (Lopez-Munoz, Alamo, & Garcia-Garcia, 2011) and introduced for clinical practice by Hoffman-La Roche in the 1960s (Fig. 1) and represent a drug class that does elicit acute anxiolysis. They are considered as anxiolytics in the narrow sense and have long been the primary focus of anxiolytic drug development. We have come a long way in the development of modern drugs to alleviate pathological anxiety. According to current international treatment guidelines for anxiety and related disorders [e.g. (Bandelow, Lichte, Rudolf, Wiltink, & Beutel, 2015; Katzman et al., 2014; Strohle, Gensichen, & Domschke, 2018)], the current recommended treatments are, as mentioned, psychotherapy and pharmacotherapy (Table 1) and their combination whereby the choice between

Table 1
Current recommendations for the treatment of anxiety and trauma-related disorders in Europe and the USA.

	GAD	SAD	PD	PTSD	OCD
SSRIs					
Citalopram	**EU**	**EU**	**EU**	*off-label*	**EU**
Escitalopram	**EU, USA**	**EU**, *USA*	**EU**	*off-label*	**EU**
Fluoxetine	*off-label*	*off-label*	**EU, USA**	*off-label*	**EU, USA**
Fluvoxamine	**EU**, *USA*	**EU, USA**	*off-label*	*off-label*	**EU, USA**
Paroxetine	**EU, USA**	**EU, USA**	**EU, USA**	**EU, USA**	**EU, USA**
Sertraline	**EU**, *USA*	**EU, USA**	**EU, USA**	**EU, USA**	**EU, USA**
SNRIs					
Desvenlafaxine		*off-label*			
Venlafaxine	**EU, USA**	**EU, USA**	**EU, USA**	*off-label*	*off-label*
Duloxetine	**EU, USA**	*off-label*	*off-label*	*off-label*	*off-label*
TCAs					
Clomipramine	*off-label*	*off-label*	**EU**, *USA*	*off-label*	**EU, USA**
Imipramine			*off-label*		
Opipramol	**EU**				
MAOIs					
Moclobemide*		**EU**			
Phenelzine			*off-label*	*off-label*	
Tranylcypromine			*off-label*		
Other antidepressants					
Mirtazapine**	*off-label*	*off-label*	*off-label*	*off-label*	*off-label*
Trazodone**				*off-label*	
Benzodiazepines					
Alprazolam	**EU, USA**	*off-label*	**EU, USA**		
Bromazepam*,**	*off-label*				
Chlordiazepoxide	**EU, USA**	*off-label*	*off-label*		
Clonazepam	*off-label*	*off-label*	**USA**		
Clorazepate	**USA**	*off-label*	*off-label*		
Diazepam	**EU, USA**	*off-label*	*off-label*		
Lorazepam	**EU, USA**	*off-label*	*off-label*		
Oxazepam	**EU, USA**	*off-label*	*off-label*		
Prazepam*,**	*off-label*				
Others					
Buspirone	**EU, USA**	*off-label*			*off-label*
D-amphetamine**					*off-label*
Gabapentin**		*off-label*			
Hydroxyzine**	**EU**				
Meprobamate	**USA**				
Pregabalin	**EU**	*off-label*			
Tramadol					*off-label*
Antipsychotics					
Trifluoperazine	**USA**				
Olanzapine**		*off-label*			
Quetiapine**	*off-label*		*off-label*	*off-label*	*off-label*

In this table only drugs are included that are approved for at least an anxiety, trauma-related or obsessive disorder in either the USA or Europe (EU) or recommended by UpToDate (https://www.uptodate.com/). **Bold typeface:** approved for the specific anxiety disorder in the USA and/or EU according to current guidelines in Europe [represented by German guidelines; (Bandelow et al., 2014; Bandelow et al., 2017; Strohle et al., 2018)]; *italic typeface:* off-label use in the USA or Europe. *Not available in the USA. **The off-label use of the listed antidepressants, antipsychotics and others that are not approved for any anxiety, trauma-related or obsessive disorder is supported by clinical studies, meta-analysis and more recent network meta-analysis [e.g. (Cipriani et al., 2018; Slee et al., 2019)].
Abbreviations: GAD: generalised anxiety disorder; MAOIs: monoamine oxidase inhibitors; OCD: obsessive compulsive disorder; PD: panic disorder; PTSD: post-traumatic stress disorder; SAD: social anxiety disorder; SNRIs: serotonin noradrenaline reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants.

the two for initial treatment depends on the availability and/or the patient's preference. These treatment guidelines are now supported by recent network meta-analyses that take into consideration not only efficacy but also tolerability in mostly indirect head-to-head comparisons of the available pharmacotherapies (Cipriani et al., 2018; Slee et al., 2019). So far, the reporting of evidence concerning the efficacy of anxiety treatments is based mainly on studies enrolling patients diagnosed by the established classification systems ICD and DSM (Bandelow & Michaelis, 2015). Selective serotonin (5-HT) reuptake inhibitors (SSRIs), including for example (es)citalopram, sertraline, fluoxetine are currently first-line drug treatment options for most anxiety disorders as they are proposed to have a better benefit/risk ratio than any other form of current pharmacotherapy (Bandelow, Michaelis, & Wedekind, 2017). Their approval as treatments in anxiety started in the early 1990s (Fig. 1). Other antidepressant drugs used in anxiety therapy include 5-HT and noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine, tricyclic antidepressants, monoamine oxidase inhibitors – and all these treatments are applied in a disorder-specific manner, although usually, monoamine oxidase inhibitors and tricyclic antidepressants are less prescribed due to safety and tolerability issues [Table 1; (Bandelow et al., 2017)]. Side effects of SSRIs include for example jitteriness at therapy onset, emotional blunting in some patients, gastrointestinal problems, insomnia, sexual dysfunction and there have been warnings concerning an increased risk of suicidal ideation (Stubner et al., 2018). While some of these symptoms improve with time, others do not. The onset of therapeutic action is delayed for

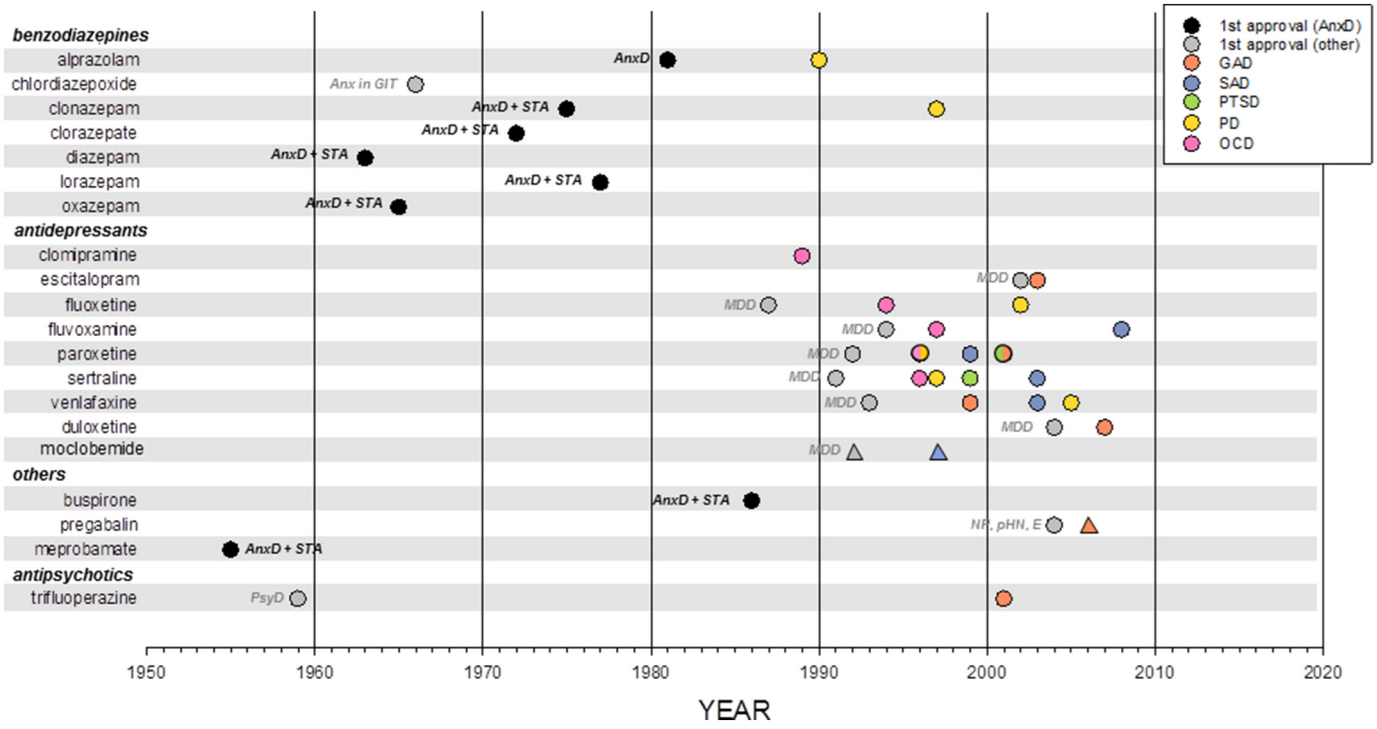

Fig. 1. Timeline of drugs approved for the treatment of specific anxiety and anxiety-related disorders by the Food and Drug Administration (FDA) of the USA (circle) or, if not by the FDA, by European authorities (triangle). The first approved indication, if different to anxiety (grey symbols) is mentioned next to the symbol. Note that the general term "anxiety disorder" when given as an indication in the 50s to 80s most closely reflects GAD. Abbreviations: Anx: anxiety; AnxD: anxiety disorder; AnxD+STA: anxiety disorders and short-term relief of the symptoms of anxiety; E: epilepsy; GAD: generalised anxiety disorder; GIT: gastrointestinal tract; MDD: major depressive disorder; NP: neuropathic pain; OCD: obsessive-compulsive disorder; PD: panic disorder; pHN: post-herpetic neuralgia; PsyD: psychotic disorder; PTSD: post-traumatic stress disorder; SAD: social anxiety disorder.

2–3 weeks or more, therefore antidepressants cannot be used as an acute anxiolytic intervention. In contrast, BDZs demonstrate efficacy for the treatment of GAD (Gomez, Barthel, & Hofmann, 2018) and are still and even increasingly prescribed (Agarwal & Landon, 2019; Bachhuber, Hennessy, Cunningham, & Starrels, 2016). In order to address concerns about side effects of BDZs in long-term treatment, including dependence, withdrawal symptoms, impaired cognition and overdose deaths (mostly in combination with alcohol), the recent recommendation in anxiety therapy has been that only patients without an active or a history of substance use disorder should be considered and treatment duration should be kept at a minimum (Baandrup et al., 2018). Also in adjunctive use, e.g. when initial combination with antidepressants is necessary, the BDZs dosage should be carefully tapered and discontinued as soon as possible to use only as needed (Gomez et al., 2018). The introduction of buspirone and moclobemide (Fig. 1) mainly for patients with GAD and SAD in Europe and the USA, respectively, has extended the list of available pharmacotherapeutic tools. In 2006/07, the two latest anxiolytic drugs, duloxetine and pregabalin, were approved by the Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) for the treatment of GAD (Fig. 1). Both appear to have a good efficacy/tolerability ratio (Slee et al., 2019).While duloxetine is (another) SNRI, the calcium channel blocker pregabalin represents a 'novel' mechanism of anxiolytic action. Despite the occurrence of somnolence and dizziness as the main side effects, pregabalin is generally well tolerated and is effective as monotherapy or as an adjunct to treatment with SSRIs/SNRIs (Baldwin et al., 2015; Generoso et al., 2017; Slee et al., 2019). However, several recent retrospective studies raise concerns about the safety of pregabalin for treating patients and, thus, it was reclassified as class C controlled substance in the UK in April 2019 [e.g. (Evoy, Covvey, Peckham, Ochs, & Hultgren, 2019; Schifano & Chiappini, 2019)]. If the mentioned standard drugs show no treatment effect when administered as mono- or polypharmacy, or if they are poorly tolerated, the use of off-label medications, including anticonvulsants (e.g. gabapentin), second-generation antipsychotics (e.g. quetiapine), sedative hypnotics (e.g. eszopiclone, ocinaplon), sympatholytics [e.g. prazosin, but see (Myers, Keller, Grubaugh, & Turek, 2019)], agomelatine, or bupropion alone or as adjuncts, may be considered; however, there is only limited empirical evidence to support their usefulness (Bandelow et al., 2017; Cipriani et al., 2018). To note, the antipsychotic quetiapine showed pronounced anxiolytic efficacy for the treatment of GAD in meta-analyses, but poor tolerability which is the likely reason why it is not approved for the indication anxiety and related disorders by both the FDA and the EMA [Table 1; (Slee et al., 2019)].

Meta-analyses across different drug treatments found response rates between 40 and 75%, with a mean of 55% (Greener, 2009; Loerinc et al., 2015; Mitte, Noack, Steil, & Hautzinger, 2005). Hence, these drugs are helpful for many to relieve the symptoms of clinical anxiety, and thus to improve quality of life. In some, but not all instances additional benefit can come from psychotherapy given together with pharmacotherapy [(Bandelow et al., 2015), see Fig. 2]. However, full clinical remission is often not achieved, a significant number of patients does not respond to treatment or they relapse after treatment cessation even after an initial positive response (Batelaan et al., 2017). Such problems suggest that current therapies are insufficient and they have rekindled the interest to develop drugs with novel mechanisms of action to improve this situation, particularly for non-responding patients.

3. Problems with, and failures in, anxiolytic drug development

In the last 50 years, there have been major efforts in academia and by pharmaceutical companies to discover new anxiolytic drugs and to explore the anti-anxiety effects of specific GABAergic (γ-aminobutyric acid), monoaminergic, glutamatergic, endocannabinoid (eCB) and neuropeptidergic agents in animals and humans (Griebel & Holmes, 2013). Unfortunately, the clinical development of many of the identified agents was discontinued for various reasons (Mandrioli & Mercolini, 2015), and since the approval of pregabalin (13 years ago) and of

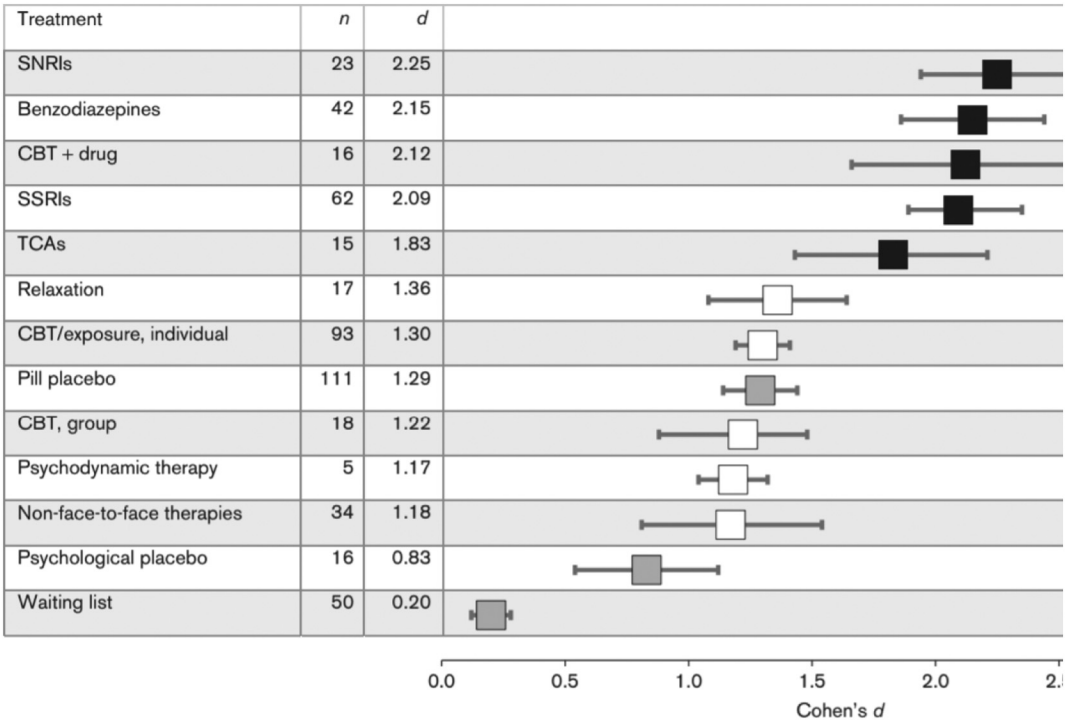

Fig. 2. Efficacy of different treatments for anxiety disorders (all anxiety disorders pooled). Pre–post effect sizes (Cohen's d) and 95% confidence intervals. Black: drugs; white: psychological therapies; grey: control groups. n, number of studies. CBT, cognitive behavioural therapy; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants [taken from (Bandelow et al., 2015) with permission, for further details see there].

duloxetine (12 years) ago (Fig. 1), no new drug has passed the EMA and/or FDA authorities to allow its use for the treatment of any anxiety or related disorder.

Anxiety and more general, central nervous system (CNS) drug development has become increasingly burdened by a number of factors, including increased cost, altered placebo responses in trials, regulatory requirements, recruitment difficulties, and many others. In general, <10% of promising CNS drug candidates identified in preclinics and taken to humans make it through the clinical development to the market and the clinical development and approval of CNS drugs takes longer than any other drug class (Kaitin, 2014, 2018). Between 50 and 60% of all failures of CNS drugs are the result of poor efficacy/efficiency, while poor safety accounts for 20–30% of failures (McArthur, 2017). This low overall success rate of compounds in clinical development is costly and has led to a 50% decline in CNS drug discovery and development programs by major pharmaceutical companies from 2009 to 2014, while university led drug discovery centres targeting neurological and psychiatric indications have increased considerably in numbers in the last years (Nutt & Attridge, 2014; Yokley, Hartman, & Slusher, 2017). In parallel, there are important ongoing discussions about how to refine our drug development pipelines (Stewart et al., 2015) and about new ways of categorising patient populations in order to improve the translation of results from animal models to clinical settings. Although anxiety disorders, and more generally mental disorders, are considered to be dimensional, most clinicians and researchers use traditional categorical classification systems, in particular the DSM-5 and ICD-10, to identify a mental disorder and to study the effects of medical interventions for these disorders. There are concerns that the use of these classification systems in anxiety drug development trials is part of the problem, since they lump together heterogeneous etiologies that may require different treatment modalities and do not consider individual differences and specific characteristics of a patient's symptomatology, and this is also reflected in the variable treatment responses within specific disorder categories (Bandelow, Reitt, et al., 2015). Consequently, initiatives have been taken – e.g. the Research Domain Criteria (RDoC) initiative by the NIMH (National Institute of Mental Health) [for review, see (Anderzhanova, Kirmeier, & Wotjak, 2017)] – to stimulate research into, and diagnosis of, the dimensions of observable behaviour and the neurobiological measures, to advance biomarker development for disease prediction and treatment response) in psychiatric conditions. The RDoC system proposes brain circuit dysfunction (see Section 4) in psychiatric disorders, rather than groups of symptoms as the organizing principle (Nicholson & Sommer, 2018). This appears to enable treatment options for individual patients' specific disorder characteristics to be refined. Similarly, in preclinical research, animal models should be viewed as a model of certain aspects of the pathology in the form of specific endophenotypes. This is not only a semantic distinction – it also promotes the use of behavioural procedures in animals as a means of examining the basis of specific behaviours relevant for anxiety and/or fear (Anderzhanova et al., 2017). The integration of refined animal models explicitly within the RDoC framework, which allows for a research agenda to focus on modelling the neurobiology of behaviours rather than disease, has only recently started to be done and will involve a more complex assessment of the experimental subject in specific test situations. Nevertheless, to realise the value of the RDoC approach, scientific findings must be integrated within the current diagnostic system to provide a diagnostic system that is stable, reliable, easy to apply and informative in terms of treatment (Schutz, 2012). Linking the two systems represents a challenge within the field, but is a promising avenue for the advancement of the diagnosis and treatment of mental disorders, including anxiety disorders. Furthermore, the fact that treating state anxiety does not necessarily reduce persistent anxiety associated with trait anxiety, and vice versa, must be taken into consideration. For example, BDZs are highly effective at reducing acute anxiety symptoms, but their long-term anti-anxiety effect is questionable (Guina & Merrill, 2018), and there is even evidence that BDZ treatment can impede the plasticity/learning changes that usually occur as a result of extinction-based cognitive behavioural therapy (CBT), and that are necessary for long-term improvements in anxiety symptoms (Hart, Harris, & Westbrook, 2010). On the other hand, SSRIs are effective at long-term control of persistent anxiety for many anxiety patients (Nabi et al., 2013), but generally have no acute effect on state anxiety and can

even increase anxiety symptoms at the beginning of treatment (as mentioned in Section 2). In preclinical studies, potential anxiolytic effects of novel compounds are mainly explored in situations involving approach-avoidance behaviour or conflicts that assess state anxiety rather than in situations involving trait anxiety (Cryan & Sweeney, 2011; Griebel & Holmes, 2013; Tasan & Singewald, 2018). Furthermore, the sensitivity of these tests is biased towards BDZ-like compounds, and they are less able to detect anxiolytic effects of (chronic) SSRI treatment (Griebel & Holmes, 2013). Finally, the fact that patient populations are very heterogeneous in terms of symptoms, sex, age, environment, diets and genetic modifications and therefore split in various subgroups needs to be taken into consideration much more (King et al., 2018; Stewart et al., 2015). In contrast, experimental animals in preclinical research are very homogeneous, being commonly biased towards young male adult subjects of (mostly) inbred strains raised in a controlled environment in terms of diet, light, temperature, humidity and many more variables (Stewart et al., 2015). Moreover, although levels of inborn anxiety-related behaviour and sensitivity to anxiolytics can differ greatly between mouse strains, this fact is scarcely taken into consideration in preclinical studies exploring the anxiolytic properties of novel drugs. One route in this direction is the utilisation of psychopathologically more relevant animal models, e.g. of hyperanxiety or of impaired fear extinction [(Sartori, Landgraf, & Singewald, 2011), see also (Flores, Fullana, Soriano-Mas, & Andero, 2018; Singewald & Holmes, 2019)]. For a better outcome of translational research in drug development, we need to consider all of these shortcomings and obstacles in the preclinical and clinical drug-discovery pipeline and, identify - via relevant endophenotypes - already early on in clinical development those groups of individuals for which the novel treatments might be most beneficial.

4. Neurobiology of fear and anxiety as a potential source of innovation and progress

During the last two decades there has been a strong push for an improved understanding of the complex mechanisms involving neuroanatomical, neurochemical, genetic and epigenetic processes that regulate anxiety and fear in both healthy and diseased states, in the belief that this knowledge would facilitate the identification of novel treatment targets (Bandelow et al., 2016; Duval, Javanbakht, & Liberzon, 2015). Clinical studies have used tools like neuroimaging, electrophysiology, genetic and epigenetic techniques, molecular analysis of post-mortem brains etc. revealing mechanisms that have gone awry in pathological anxiety and anxiety patients [e.g.(Craske et al., 2017; Maron, Lan, & Nutt, 2018; Rasmusson & Pineles, 2018; Schiele & Domschke, 2018; Starke, Fineberg, & Stein, 2019; Taylor & Whalen, 2015)]. Although there was tremendous progress, the neurobiology underlying anxiety, and in particular maladaptive anxiety, and the exact mechanisms of therapeutic treatments, still remain incompletely understood. Complementary approaches use research in animal models to study anxiety mechanisms, paving the way for gaining information on aetiology and treatment of anxiety-related disorders in humans (Kas et al., 2011; Sartori et al., 2011). Since anxiety, fear learning and extinction mechanisms are conserved remarkably well across species (Cryan & Holmes, 2005; Shin & Liberzon, 2010; Tasan & Singewald, 2018), research involving animal models – in particular, specific psychopathologically more relevant fear and anxiety models (see Section 3) – in combination with similar analysis techniques as used in humans adapted for the model organism, is of clear translational value. However, there are important constraints in this translation such as the uniqueness of human endophenotypes, cognitive traits, processes and brain structures that have been highlighted in various reviews [see e.g.: (Andrews, Papakosta, & Barnes, 2014; Cryan & Sweeney, 2011; Flores et al., 2018; Freudenberg, O'Leary, Aguiar, & Slattery, 2018; Haller, Aliczki, & Gyimesine Pelczer, 2013; Harro, 2018; Stewart & Kalueff, 2014; Tasan & Singewald, 2018)]. With these precautions in mind, basic anxiety-related processes are increasingly being identified and successfully replicated in other species including humans (Stewart et al. 2014; Mohammad et al. 2016).

4.1. Circuitry

At the neuroanatomical level, partially overlapping key networks consisting of, but not limited to, several critical brain regions seem to be important for the processing, memory and expression of fear- and anxiety-related behaviour (Fig. 3). Specifically, the amygdala, which receives inputs e.g. from the thalamus, the medial prefrontal cortex (mPFC), and the hippocampus, modulates corresponding behavioural and physiological responses via projections that extend from its central nucleus to multiple regions, including the hypothalamus, the bed nucleus of the stria terminalis, the brainstem and the periaqueductal grey, that finally elicit defensive anxiety and/or fear responses (Calhoon & Tye, 2015; Farb & Ratner, 2014; Goodkind & Etkin, 2018; Knight & Depue, 2019; Li & Lee, 2018; Singewald, 2007; Tovote, Fadok, & Luthi, 2015). These brain areas often consist of several subregions and/or microcircuits such as parts of the amygdala and the bed nucleus of the stria terminalis that can exert functionally distinct, even opposing roles in anxiety. Here, the development and use of optogenetics, designer receptors exclusively activated by designer drugs (DREADDs), and other approaches have provided the possibility to control the activity of specific neuron populations and projections in the brain and assess their functional impact on anxiety- and fear-related behaviour. These methods have been crucial in providing more detailed insights into relevant neurocircuitries and, thus, in identifying potential circuitry-based targets for treating anxiety disorders (Dias, Banerjee, Goodman, & Ressler, 2013; Griebel & Holmes, 2013).

One fundamental idea regarding the mechanisms in the development of anxiety disorders is that there are scrambled brain connections, chemical imbalances and dysbalanced processes in relevant neurocircuitries, for example between those that promote aversive responding, favouring fear learning and maintenance vs. those that inhibit aversive processing and favour inhibitory (extinction) learning. These alterations are produced by endogenous (e.g. genetic) and exogenous (e.g. environmental, epigenetic) factors [(Fenster, Lebois, Ressler, & Suh, 2018), see below]. Treatments including pharmacotherapy work by restoring balance in affected neurochemistry and circuitries (Carlisi & Robinson, 2018). For example, alterations in the structure, function and connectivity of the amygdala, the mPFC, the anterior cingulate cortex and the insula as well as more recently the bed nucleus of the stria terminalis [due to advances in the imaging techniques (Robinson, Pike, Cornwell, & Grillon, 2019)] are suggested to contribute to the development and maintenance of anxiety disorders in humans (Duval et al., 2015; Etkin & Wager, 2007; Fox & Kalin, 2014; Goodkind & Etkin, 2018; McLaughlin et al., 2014; Robinson et al., 2019; Xu et al., 2019; Young & Craske, 2018). Further maladaptations in other brain areas, including the thalamus and the striatum, have been observed in an anxiety disorder-specific manner (Brooks & Stein, 2015). In particular, pathologically heightened fear/anxiety seems to be commonly associated with increased amygdala activation in response to negative emotional stimuli (Etkin & Wager, 2007). Enhanced amygdala responsivity is often associated with hyperactivity in a network that mediates the anticipation of negative outcomes and consists of the anterior cingulate cortex, insula, dorsolateral PFC and the medial orbitofrontal cortex, and hypoactivity in inhibitory systems, for example involving the ventromedial PFC, which is implicated in top-down inhibition of amygdala output [Fig. 3; see e.g. (Schmidt, Khalid, Loukas, & Tubbs, 2018; Tovote et al., 2015)]. This control of the ventromedial PFC [in humans; the homologous region in rodents is the infralimbic cortex (IL)] over the amygdala is important in modulating negative bias in anxiety (Carlisi & Robinson, 2018) or in fear extinction, a key fear-inhibitory mechanism underlying exposure-based therapy (EBT) [Section 8; (Heilbronner, Rodriguez-Romaguera, Quirk, Groenewegen, & Haber, 2016; Sartori & Singewald, 2017)]. A particular challenge of

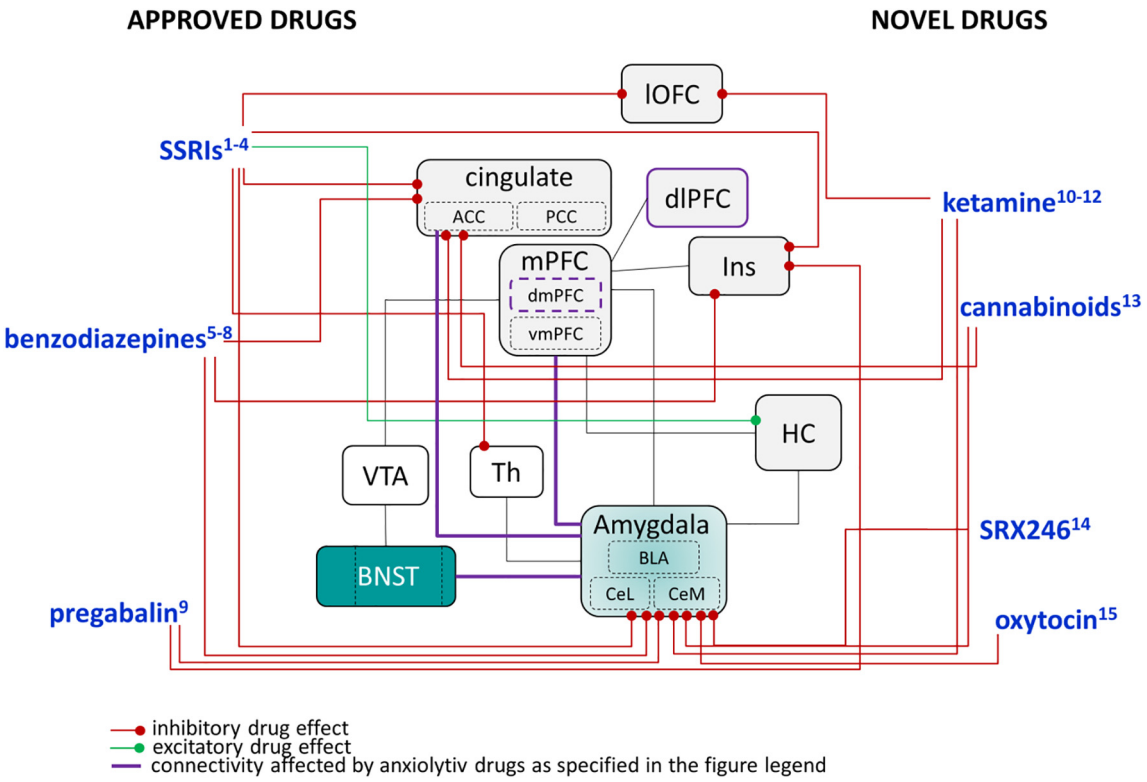

Fig. 3. Proposed putative sites of actions within anxiety-relevant brain circuitries by approved (left side) and novel (right side) anxiety-attenuating drugs. This is a selection of examples and by no means a complete summary. The proposed anxiety neurocircuitry depicted is obtained by findings in preclincial and clinial research [more detailed information in (Calhoon & Tye, 2015; Robinson et al., 2019; Schmidt et al., 2018; Tovote et al., 2015). Some of the brain areas such as the BNST, amygdala, and PFC are partitioned into subregions that can mediate distinct and sometimes even opposite functions (e.g. anxiogenic vs. anxiolytic). In patients with anxiety or anxiety disorders, dysfunctional regulation in this circuitry is evident [see Section 3 and (Etkin & Wager, 2007; Robinson et al., 2019; Schmidt et al., 2018; Tovote et al., 2015)] for review. Inhibitory (red lines) and excitatory (green lines) effects of anxiety-reducing drugs on activity in different brain areas have been observed. Mainly studies in anxiety patients were considered here. Only when there was no or limited information available, drug studies in healthy individuals, patients with major depression or animals were used [for further information see Section 5 and findings/references in [1](Gimenez et al., 2014), [2](Phan et al., 2013), [3](Schmidt et al., 2018), [4](Kraus, Castren, Kasper, & Lanzenberger, 2017), [5](Brown et al., 2015), [6](Leicht et al., 2013), [7](Schunck et al., 2010), [8](Wise et al., 2007), [9](Aupperle et al., 2011), [10](Sterpenich et al., 2019), [11](Downey et al., 2016), [12](Gass et al., 2019), [13](Rabinak & Phan, 2014), [14](Lee et al., 2013), [15](Gao et al., 2016)]. Important research has also found effects of anxiety treatments on network connectivity. This kind of research is increasingly evolving, some first examples indicated in the figure with purple lines are: findings of a reduced dmPFC/dorsal ACC-amygdala or amygdala-BNST connectivity following treatment with SSRIs (Grillon, Robinson, Cornwell, & Ernst, 2019; Robinson et al., 2019), an increased connectivity between the rostral ACC and the amygdala after adminstration of a benzodiazepine (Leicht et al., 2013) and increased global brain connectivity in the dmPFC and dlPFC following a single ketamine infusion (Abdallah et al., 2018). **Abbreviations:** ACC: anterior cingulate cortex; BLA: basolateral amygdala; BNST: bed nucleus of the stria terminalis; CeL: lateral part of the central amygdala; CeM: medial part of the central amygdala; dlPFC: dorsolateral prefrontal cortex; dmPFC: dorsomedial prefrontal cortex; HC: hippocampus; Ins: insula; mPFC: medial prefrontal cortex; lOFC: lateral orbitofrontal cortex; PCC: posterior cingulate cortex; SSRIs: selective serotonin reuptake inhibitors; Th: thalamus; vmPFC: ventromedial prefrontal cortex; VTA: ventral tegmental area.

basic and clinical human neuroscience is to better understand circuit-level causality, for example between the function of a circuit and resulting behaviour or dysfunction of that circuit and anxiety symptoms.

Medical interventions, including SSRIs [e.g.(Doruyter et al., 2016; Schmidt et al., 2018)], and other pharmacological treatments (Fig. 3), as well as (exposure-based) CBT [e.g. (Brooks & Stein, 2015; King et al., 2016; Neufang et al., 2019; Steiger et al., 2017); see scheme in Excursus 2 in (Sartori & Singewald, 2017)] have been shown to affect and in part normalise important aspects of such dysfunctions and imbalances, as revealed mainly by functional brain imaging. These observations could serve as part of biomarkers predicting disease vulnerability/onset and/or a patient's response to a specific type of therapy [e.g. (Ball, Stein, Ramsawh, Campbell-Sills, & Paulus, 2018; Bandelow et al., 2016; Frick et al., 2018; Lueken et al., 2016; Pitman et al., 2012). Increasing evidence suggests that these circuitry treatment effects are mediated by changes in synaptic plasticity in key areas of the circuitry (Krystal et al., 2017; Luchkina & Bolshakov, 2018; Mahan & Ressler, 2012; Mansson et al., 2016; Mansson et al., 2017). Research has provided some insight into which genetic and epigenetic mechanisms (Bandelow et al., 2016; Ziegler, Schiele, & Domschke, 2018) act (and interact) to produce such plastic changes, and in particular which neurochemical mechanisms are involved. Current approaches such as antidepressants or CBT produce plastic changes after chronic treatment only. However, there is evidence that changes in neuroplasticity (e.g. changes in neurite growth, dendritic spine density, synapse number, intrinsic excitability, etc) important to reshape circuitries and connectivity can be produced even within 24 hours by compounds including ketamine, psychedelics and *N*-methyl-D-aspartate (NMDA) receptor partial agonists [Fig. 3; (Olson, 2018). While circuit psychiatry - also with other means (e.g. tailored neuroplasticity-inducing interventions through transcranial magnetic stimulation) - is on the horizon (Dias et al., 2013), there is still a lot to be learned utilizing such plasticity promoting neurotherapeutics to address the circuitry abnormalities identified. Research for maximizing efficacy while minimizing deleterious effects opens up the potential for the development of novel, personalized, circuit-based interventions in the treatment of anxiety and related disorders.

4.2. Genetics and epigenetics

Family and twin studies have indicated that anxiety disorders are multifactorial in cause, involving an interaction between multiple genetic and environmental factors. Genetics has been and is still hoped to offer entirely new targets in anxiety treatment, although it is getting more apparent that - due to the polygenetic complexity of anxiety

disorders - it will take much more time than envisioned until the information gathered will be able to translate into new medicines. In the last decades, clinical genetics have been able to identify various susceptibility genes, including the 5-HT transporter 5-HTT, 5-HT_{1A} receptor, monoamine oxidase A, catechol-*O*-methyltransferase, phosphodiesterase 4B and the brain-derived neurotrophic factor (BDNF) gene, involved in specific anxiety-relevant phenotypes and/or in in the aetiology and maintenance of pathological anxiety in a non-specific or disorder-dependent manner (Alisch et al., 2017; Bandelow et al., 2016; Gottschalk & Domschke, 2017; Meier et al., 2019; Savage, Sawyers, Roberson-Nay, & Hettema, 2017; Smoller, 2016; Ziegler et al., 2018). In addition, gene-gene interactions, as for example between variants of the CB_1 receptor (CNR1) promoter and the functional polymorphism of the 5-HT transporter, may differentially affect anxiety and the vulnerability to side effects of drugs in humans [for review see (Lazary, Juhasz, Hunyady, & Bagdy, 2011)]. What is known so far, is that the contributions of each of these and additional genetic variants to disease risk are small (1–2%) and sum up to moderate heritability (e.g. 30% in GAD) of anxiety disorders, suggesting a considerable role for environmental factors (such as stress) and the epigenome (Hettema, Prescott, Myers, Neale, & Kendler, 2005). Evidence indicates that different types of recent life stressors and negative life events may cause similar anxiety symptoms in humans by different neurobiological pathways [see e.g., (Gonda et al., 2019; Hassell Jr., Nguyen, Gates, & Lowry, 2018)]. This advocates selective treatment approaches after certain stressors, rather than the blockbuster strategy of the past (see also Section 10). The role of epigenetics as modulatory factors between the genetic predisposition and environmental experiences (Kuehner, Bruggeman, Wen, & Yao, 2019) has been increasingly recognized in anxiety (Alisch et al., 2017; Wang, Lou, & Wang, 2019). For instance, altered DNA methylation patterns in GAD (Gottschalk & Domschke, 2017), PD (Iurato et al., 2017) or adolescents with anxiety disorder (Bortoluzzi et al., 2018) have been found. Information derived from altered genetic and epigenetic profiles in anxiety may be useful markers of disease and/or treatment response. Furthermore, epigenetics are hoped to offer an additional pool of innovative targets for the future development of anxiety-disorder treatments (Bartlett, Singh, & Hunter, 2017; Graff et al., 2014; Hemstedt, Lattal, & Wood, 2017; Nieto, Patriquin, Nielsen, & Kosten, 2016; Regue-Guyon, Lanfumey, & Mongeau, 2018). For example, microRNAs as fine tuners of gene expression at the post-transcriptional level have emerged as critical regulators of anxiety and fear as well as of treatment success in preclinical studies (Murphy & Singewald, 2018; Scott et al., 2015). Likewise, histone-deacetylase inhibitors may be useful in anxiety disorders, by promoting relevant gene expression (Sah et al., 2019; Tran, Schulkin, Ligon, & Greenwood-Van Meerveld, 2015; Whittle & Singewald, 2014) and targeting also some common comorbidities of anxiety disorders (Moloney, Stilling, Dinan, & Cryan, 2015). At present the study of epigenetic drug targets for anxiety remains in its infancy, and it is not clear yet whether these agents actually offer superior outcomes to existing treatments.

4.3. Neurochemistry

More traditional pharmacotherapeutic approaches have targeted identified neurochemical imbalances. In general, multiple neurotransmitter/-modulator systems which often show great system diversity in expression, together with their receptors contribute to the highly complex and precise regulation of anxiety and fear. These include monoaminergic, GABA-ergic, glutamatergic, neuropeptidergic and eCB systems and there is evidence for dysregulation in each of these systems in a variety of brain regions of different anxiety-related disorders [e.g. (Bandelow et al., 2016; Maron et al., 2018). The precise understanding of relevant neurochemical imbalances in each of the different anxiety disorders provides a valuable resource for rational improvement of pharmacotherapeutic approaches. While classical anxiety-related neurotransmitter target systems modulating anxiety-related neurochemistry (monoamines, GABA) have evolved from serendipitous observations, novel target systems, including the glutamate system, eCBs, neuropeptides and neurosteroids, have been identified more directly through preclinical work and have been or are now investigated in clinical trials (see Section 6 and 8). In addition to the neurotransmitter/-modulator systems studied in clinical trials and therefore addressed in this review, many other promising mechanisms and targets for exerting anxiolytic effects have been proposed in preclinical research but have not been processed into the clinics or else are at the beginning of clinical investigations. These include metabotropic glutamate receptor (mGluR) transmission [Table 2; (Ferraguti, 2018)], the microbiome (Lach, Schellekens, Dinan, & Cryan, 2018; Leclercq, Forsythe, & Bienenstock, 2016), neuroinflammation (Furtado & Katzman, 2015; Kim & Jeon, 2018), epigenetics (Whittle & Singewald, 2014), cellular/mitochondrial metabolism (Hollis et al., 2015) and oxidative stress (Fedoce et al., 2018; Hassan, Silva, Mohammadzai, da Rocha, & LF, 2014) among others (Garcia-Garcia, Newman-Tancredi, & Leonardo, 2014).

For example, neuroinflammation has recently been recognized as a potential pathophysiological mechanism contributing to the onset and/or maintenance at least in subgroups of anxiety patients, opening the possibility to propose immune-targeting interventions as complementary or alternative routes of treatment (Furtado & Katzman, 2015; Gaspersz et al., 2017; Kim & Jeon, 2018). Stress seems to be an important exacerbating factor and an activated immune system is thought to be involved in mediating some of its detrimental effects, e.g. on neurogenesis and synaptogenesis. Evidence in support of an involvement of inflammation in anxiety disorders has been gained so far mainly by investigating peripheral levels of cytokines, e.g. in GAD (Costello, Gould, Abrol, & Howard, 2019), PD (Petrowski, Wichmann, & Kirschbaum, 2018), PTSD (Passos et al., 2015) and OCD (Rao et al., 2015) patients. Immune targeting interventions to produce anxiolytic effects are just beginning to evolve with some interesting indicative preliminary findings involving classical (Makunts, Cohen, Lee, & Abagyan, 2018) and non-classical multitarget anti-inflammatory agents with anxiolytic properties such as N-acteylcysteine (Santos, Herrmann, Elisabetsky, & Piato, 2019). Another system potentially relevant for future anxiety treatment and likely interlinked with the inflammatory system is the brain-gut axis, and in particular the microbiome. Disturbances in the composition of the microbiome have been linked to anxiety (Lach et al., 2018; Leclercq et al., 2016) and treatments aimed at normalising these disturbances using specific probiotics have been proposed (Yang, Wei, Ju, & Chen, 2019). Other microbial-based approaches include prebiotics [dietary components that promote the growth of beneficial bacteria; (Burokas et al., 2017)] and post-biotics [microbial metabolites; (van de Wouw et al., 2018)] as well as potential fecal microbiota transplantation (Kang et al., 2019). Defining the utility of such inflammation/microbiome-targeted approaches for clinical anxiety populations, and revealing criteria to identify the most suitable recipients will be important challenges in the future on the way to improved personalized anxiety treatment.

The growing knowledge concerning neurobiological mechanisms of anxiety and anxiolytic drug action supports drug development for anxiety-related disorder. We now present and discuss a number of those drug candidates with clinical promise (Tables 2 and 3).

5. Novel compounds acting on refined classical pharmacological target systems

5.1. Monoamine systems

5-HT, together with noradrenaline and dopamine are the classical monoamine neurotransmitters that regulate many different physiological and behavioural functions, including anxiety, mood, aggression, stress responses and additional aspects of emotionality. Many of the current medical treatments of anxiety disorders, such as SSRIs, SNRIs,

Table 2
Synopsis of drugs currently in clinical development for the treatment of anxiety and anxiety-related disorders.

Drug	Other names	Company	Main mechanisms of action	Marketed for	Phase	Indication	Ongoing trials	Comments
Monoamine system								
Vilazodone		Forest Laboratories	5-HT_{1A} PAG > SERT-I	MDD	2	SAD	NCT01712321	
AVN-101		Avineuro Pharmaceuticals	5-HT_7,H_1, α_{2B} ANTG > 5-$HT_{2C,2A,6}$, $\alpha_{2A,2C,1B}$ ANTG > 5-$HT_{2B,5A}$, α_{1A} ANTG > 5-HT_{1A}, H_2, α_{1D} ANTG		2	AD	Recruiting, http://www.avineuro.com/363/	
Brexpiprazole		Otsuka Pharmaceuticals Lundbeck A/S	PAG: 5-HT_{1A}, $D_{2,3}$, ANTG: 5-$HT_{2A,7}$, $\alpha_{1B,2C}$ > ANTG: 5-HT_{2B}, $\alpha_{1A,1D}$ > PAG: 5-HT_{2C}, ANTG: 5-HT_6, $\alpha_{2A,2B}$, β, H_1	MDD, schizophrenia	2	PTSD	NCT03033069	Completed in November 2018
Gepirone ER	Travivo®	Fabre-Kramer Pharmaceuticals	5-HT_{1A} PAG		3	GAD	https://www.fabrekramer.com/products/	
FKW00GA	TGW00AA	Fabre-Kramer Pharmaceuticals	5-HT_{1A} PAG, 5-HT_{2A} ANTG		2 2	SAD GAD	https://www.fabrekramer.com/products/tgw00aa/	
Cyclobenzaprine VLD	TNX-102 KRL-102 Tonmya®	Tonix Pharmaceuticals	α_{1A}, H_1 ANTG >NET-I > 5-HT_{2A} ANTG	musculoskeletal pain, spasm	3	PTSD	NCT03508700, NCT03841773	
Psilocybin			5-$HT_{2A,2C}$ PAG > 5HT_{1A} PAG		2	LTA	NCT00957359	Psychotherapy assistance
					2	OCD	NCT03356483, NCT03300947	
LSD			5-$HT_{1A,2A,2B,2C}$ PAG > α_{1A}, D_2 PAG > > $D_{1,3}$, α_{2A} PAG		2	LTA	NCT03153579	CBT assistance
MDMA			NET-I > SERT-I > DAT-I, TAAR1 AG, VMAT-I		2 3	LTA PTSD	NCT02427568 NCT03282123, NCT03485287, NCT03752918, NCT03537014	CBT assistance CBT assistance
Propranolol			$\beta_{1,2}$ ANTG	hypertension, angina pectoris, atrial fibrillation, myocardial infarction, migraine, essential tremor, hypertrophic subaortic stenosis, pheochromocytoma	2 2/3	PD PTSD	NCT02631694 NCT03152175, NCT01713556, NCT03151681, NCT02789982, NCT03251326	CBT assistance
Doxazosin			α1 ANTG	hypertension, benign prostatic hyperplasia	1/2	PTSD	NCT02308202, NCT02500602, NCT03339258, NCT02492334	EBT assistance
L-DOPA			dopamine precursor	Parkinson's disease	2 (4)*	PTSD	NCT02560389	EBT assistance, completed in February 2019
Modafinil			weak DAT-I	hypersomnia, narcolepsy	2/3	PTSD	NCT01726088	
Vortioxetine		Sinopharm	SERT-I, 5-HT_3 ANTG >5-HT_{1A} AG, 5-HT_{1B} PAG, 5-$HT_{1D,7}$ ANTG > > NET-I	MDD	disc. 2 (4)* 2 (4)*	GAD SAD PTSD	 NCT02294305 NCT02637895	 MDD with SAD
GABA system								
Aloradine	PH94B	VistaGen Therapeutics	human vomeronasal receptor modulator, GABA-AR PAM		3	SAD	1st half 2019	
Pregnenolone			CB_1 NAM, MAP2 ligand, PXR AG	formerly: rheumatoid arthritis	2 2	PTSD OCD	NCT03799562 NCT01949753	 CBT assistance
Glutamate system								
Ketamine			NMDAR ANTG	anaesthetic	2/3 1 1 2	PTSD arachnophobia SAD OCD	NCT02655692, NCT02577250, NCT02397889, NCT02727998, NCT02766192 ACTRN12618001381279p NCT02083926 NCT02624596	EBT assistance, timber psychotherapy GABA, Glu, circuit- and network synchrony

(continued on next page)

Table 2 (*continued*)

Drug	Other names	Company	Main mechanisms of action	Marketed for	Phase	Indication	Ongoing trials	Comments
NBTX-001	xenon	Nobilis Pharmaceuticals	NMDAR ANTG		2/3	PTSD	NCT03635827	
RGH-618		Gedeon Richter	$mGluR_{1,5}$ NAM		1	AD	EudraCT2011–005865-19	
D-cycloserine			NMDAR PAG	tuberculosis	1	SAD	NCT02066792, NCT02099825	CBT assistance EBT assistance
					2 (4)*	OCD	NCT02656342	EBT assistance
					2/3	PTSD	NCT00875342, (NCT03216356)	CBT assistance
					1	PD	NCT01944423	CBT assistance, completed in February 2019
NYX-783		Aptinyx	NMDAR MOD		1/2	PTSD	2nd half of 2019	EBT assistance?
lanicemine	AZD6765	AstraZeneca	NMDAR ANTG		1	PTSD	NCT03166501	
Voltage-gated ion channels								
Riluzole oral			SC-I, NMDAR ANTG, GluT activator	amyotrophic lateral sclerosis	1/2	PTSD	NCT02155829, NCT02019940	
Riluzole sublingual	BHV-0223	Biohaven Pharmaceutical Holding Company	SC-I, NMDAR ANTG, GluT activator	amyotrophic lateral sclerosis	2/3 NDR	SAD GAD	NCT03017508	
Troriluzole	BHV-4157 FC 4157 trigriluzole	Biohaven Pharmaceutical Holding Company	SC-I, NMDAR ANTG, GluT activator		2/3 3	OCD GAD	NCT03299166 NCT03829241	
Endocannabinoids								
Cannabis						anxiety/GAD	NCT03491384	
Cannabidiol			5-HT_{1A} PAG, 5-HT_{2A} AG, 5-HT_3 ANTG, CB_1 NAM, CB_2 IAG, $TRPV_{1,2}$ AG, FAAH-I PPARγ AG		2/3	anxiety/GAD SAD PD PTSD agoraphobia	NCT02548559, NCT03549819 NCT03549819, NTR5100 NCT03549819, NTR5100 NCT03518801, NCT02517424 NCT03549819	
Nabilone	Cesamet		$CB_{1,2}$ AG		1/2	OCD	NCT02911324	EBT assistance, RPT assistance
Marijuana			THC: $CB_{1,2}$ AG, CBD: see above		1/2 2	OCD PTSD	NCT03274440 NCT02759185, NCT02874898	Completed in January 2019, EBT assistance
JNJ-42165279		Janssen-Cilag	FAAH-I		2	AD	NCT02498392, EudraCT2015-002007-29	
					2	SAD	NCT02432703	Completed in October 2018
Neuropeptides								
SRX-246	*API-246*	Azevan Pharmaceuticals	V_{1A}R ANTG		2 1	PTSD AD	NCT02733614 NCT03036397, NCT02922166	
Oxytocin			OTR > > V_{1A} R AG	labour induction, stimulation of milk production	2 (4)*	PTSD	NCT02469259, NCT02742532, NCT03211013, NCT03875391	Completed January 2019
					2	anxiety	NCT03566069	Psychotherapy assistance
Suvorexant			$OX_{1,2}$R ANTG	insomnia	2 (4)* 2 (4)*	PD PTSD	NCT02593682 NCT02849548, NCT02704754, NCT03642028	
Neuropeptide Y			$Y_{1,2,5}$ AG		1	PTSD		

Hormones						
Mifepristone	PR ANTG> > GR ANTG	Pregnancy termination	1	Anxiety disorders	NCT02099825	Psychotherapy assistance with DCS
Phytochemicals						
Echinacea angustifolia			2	GAD	NCT03463018	
Galphimia glauca	NMDAR ANTG		2	GAD	NCT03702803	Completed early 2019

Abbreviations: >: greater affinity/potency; >>: much greater affinity/potency; 5-HT: serotonin; α: alpha-adrenoceptor; AD: anxiety disorder; AG: agonist; ANTG: antagonist; β: beta-adrenoceptor; CaC: calcium channel; CBT: cognitive behavioural therapy; D_2R: dopamine 2 receptor; DCS: d-cycloserine; disc.: discontinued; EBT: exposure-based therapy; EudraCT: European Clinical Trials Database; FAAH: Fatty acid amide hydrolase; ER: extended release; GABA: γ-aminobutyric acid; GABA-AR: GABA-A receptor; GAD: generalised anxiety disorder; Glu: glutamate; GluT: glutamate transporter; GR: glucocorticoid receptor; H_1R: histamine H1 receptor; I: inhibitor; IAG: inverse agonist; LTA: life-threatening anxiety; M: modulator; MAP2: microtubule-associated protein 2; MDD: major depressive disorder; $mGluR_{1,5}$: metabotropic glutamate receptor 1,5; MTR: Melatonin receptor; NAM: negative allosteric modulator; NDR: no development reported; NMDAR: *N*-methyl-D-aspartate receptor; NTR: Netherlands Trial Register; OCD: obsessive compulsive disorder; $OX_{1,2}$R: orexin 1,2 receptor; OTR: oxytocin receptor; PAG: partial agonist; PD: panic disorder; PDE7: Type 7 cyclic nucleotide phosphodiesterase inhibitor; PPARγ: peroxisome proliferator-activated receptor gamma; PR: progesterone receptor; PTSD: post-traumatic stress disorder; PXR: pregnane X receptor; RPT: response prevention therapy assistance; SAD: social anxiety disorder; SC: sodium channel; SERT: serotonin transporter; TAAR: trace amine-associated receptor; THC: Δ^9-tetrahydrocannabinol; TRPV: transient receptor potential cation channel subfamily V member; V_{1A}R: vasopressin receptor 1A; VLD: very low dose; VMAT: vesicular monoamine transporter; Y: neuropeptide Y receptor. The index * refers to clinical trials indicated as Phase 4 trials in clinicaltrials.gov

tricyclic antidepressants, monoamine oxidase inhibitors and buspirone (Table 1), indeed affect 5-HT (and other monoamine) neurotransmission, as do psychedelic drugs, including psilocybin, dimethyltryptamine and lysergic acid diethylamide (LSD), which are discussed as potential future anxiety treatments in Section 8. As mentioned, SSRIs in particular are recommended as first-line treatment for various different anxiety disorders (Table 1). The role of 5-HT and SSRIs in anxiety is complex and the mechanisms of 5-HT-associated anxiolytic actions are still not fully understood. An important aspect is that 5-HT signalling is known to modulate the communication between key constituents of fear and anxiety circuitries (Babaev, Piletti Chatain, & Krueger-Burg, 2018; Carhart-Harris & Nutt, 2017). For example, one proposed network action of SSRIs involves diminishing anxiety-relevant negative bias in a 'bottom-up' manner, by altering amygdala and anterior cingulate cortex reactivity to negative cues targeting subcortical regions of the so-called survival circuitries that are implicated in anticipation, reactivity, regulation and learning of affective cues [Fig. 3; (Young & Craske, 2018)]. In principle, the enhancement of 5-HT concentrations in the synaptic cleft through the use of SSRIs can activate any of 14 different G-protein-coupled 5-HT receptors ($5\text{-HT}_{1A\text{-}F}$, $5\text{-HT}_{2A\text{-}C}$, 5-HT_4, $5\text{-HT}_{5A\text{-}B}$, 5-HT_6, 5-HT_7) and of the three 5-HT_3 receptor subtypes A-C in the brain, which are ligand-gated ion (Na^+, Ca^{2+}, K^+) channels. This high diversity of 5-HT receptors, together with their presynaptic or postsynaptic localisation in specific brain areas, underscores the difficult clarification of their complex roles in the regulation of anxiety-relevant brain circuits and behaviour. It has been suggested that stimulation of 5-HT_{2B} and the blockade of 5-HT_{2A}, 5-HT_3, and probably 5-HT_{5A} receptors are important for inducing anxiolytic effects. The contributions of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_4, 5-HT_6 and 5-HT_7 receptors are still not entirely clear, as anxiolytic effects are observed after both their stimulation and their blockade in a brain-area-dependent manner [see (Zmudzka, Salaciak, Sapa, & Pytka, 2018) for a recent review]. Concerning for example the complex contribution of 5-HT_{1A} receptors, stimulation of presynaptic 5-HT_{1A} autoreceptors in the raphe nuclei and of postsynaptic 5-HT_{1A} heteroreceptors in the cortex has been shown to cause anxiolytic effects whereas activation of postsynaptic 5-HT_{1A} receptors in the hippocampus triggers anxiogenic responses (Garcia-Garcia et al., 2014; Olivier, 2015; Yamashita, Rosa, Lowry, & Zangrossi Jr., 2019; Zmudzka et al., 2018). Moreover, different serotonergic pathways affect anxiety-like, anti-depressant and anti-impulsive behaviour (Ohmura et al., 2019). Apart from investigating mechanisms of anxiety-related actions, a contribution of specific 5-HT receptors to the various adverse effects of SSRIs has been proposed, such as for example sexual dysfunction [5-HT_{1A}; (Olivier, 2015)] or a paradoxical anxiogenic response to subchronic SSRI treatment (Turcotte-Cardin et al., 2019). The knowledge about such diverse activity profiles of 5-HT receptors is important for the development of compounds specifically exerting agonistic and/or antagonistic properties at one or more receptors in order to increase anxiolytic efficacy and reduce the occurrence of side effects. A partial agonist strategy may be as well an option providing that these substances sufficiently activate "anxiolytic" and sufficiently block "anxiogenic" receptor subpopulations. Buspirone, approved for the treatment of GAD (Table 1, Fig. 1) is an example of such a strategy. An alternative concept is represented by biased agonists preferentially activating specific receptor subpopulations. For example, F13714 is a substance that acts as a full agonist at presynaptic 5-HT_{1A} receptors only and exerts anxiolytic and fear-reducing effects in animals (Depoortere, Bardin, Varney, & Newman-Tancredi, 2019; Zhao et al., 2019), but has not been tested in humans so far. However, how these strategies finally translate into the clinics, is not entirely clear due to the complex regulation of the 5-HT system upon pharmacological intervention causing adaptations in receptor expression and 5-HT release. We now present examples of such attempted refinement of monoaminergic, in particular serotonergic, compounds that are in clinical development with some promise for anxiety treatment.

Table 3
Overview of drugs in development for the treatment of anxiety- and related disorders, listed according to the studied anxiety-related disorders and current phase of clinical development.

Indication	Clinical Phase of Development		
	III	II	I
GAD	Cannabidiol Troriluzole Vilazodone	AVN-101 FKW00GA Gepirone ER (Travivo®) Echinacea angustifolia Galphimia glauca	
SAD	Aloradine Cannabidiol D-cycloserine Gepirone ER (Travivo®) Riluzole sl (BHV-0223)	FKW00GA JNJ-42165279 Vilazodone	D-cycloserine Ketamine
Specific phobias	Cannabidiol		Ketamine
PD	Cannabidiol	D-cycloserine Propranolol Suvorexant	
PTSD	Brexpiprazole Cyclobenzaprine VLD (Tonmya®) D-cycloserine Ketamine MDMA Modafinil NBTX-001	Cannabidiol Doxazosin L-DOPA Marijuana NYX-783 Oxytocin Riluzole oral SRX-246 Suvorexant Vortioxetine	Lanicemine Neuropeptide Y NYX-783
OCD	D-cycloserine Troriluzole	Ketamine Marijuana Nabilone Psilocybin Troriluzole	Psilocybin
LTA		LSD MDMA Psilocybin	
Anxiety disorders		AVN-101 Cannabidiol JNJ-42165279 Oxytocin Vortioxetine	RGH-618 SRX-246

Drugs are presented in alphabetical order. **Abbreviations:** ER: extended release; GAD: generalised anxiety disorder; LTA: life-threatening anxiety; mod: modulator; OCD: obsessive compulsive disorder; PD: panic disorder; PTSD: post-traumatic stress disorder; SAD: social anxiety disorder; sl: sublingual; VLD: very low dose.

5.1.1. Vilazodone

Vilazodone is a 5-HT reuptake inhibitor and 5-HT_{1A} receptor partial agonist that is proposed to more powerfully elevate 5-HT levels than pure SSRIs do. It was approved for the treatment of adult major depression by the FDA in 2011. Prompted by evidence of anxiolytic properties of vilazodone in patients with depression (Thase, Chen, Edwards, & Ruth, 2014), recent meta-analyses asserted that vilazodone was superior to placebo in the short-term treatment of GAD, with small effect sizes (Slee et al., 2019; Stuivenga et al., 2019; Zareifopoulos & Dylja, 2017), whereby early improvements in anxiety scores with the drug might predict a positive response and facilitated remission in GAD [(Clayton et al., 2017)]. The therapeutic effects were already observed after two weeks of treatment. Although there is little evidence of sexual dysfunction (Shi, Wang, Xu, & Lu, 2016) and of treatment-emergent suicidal ideation (Thase et al., 2017), patients were more likely to discontinue drug than placebo treatment due to the occurrence of adverse events, including nausea and diarrhea (Slee et al., 2019; Zareifopoulos & Dylja, 2017). This observation is in contrast to evidence derived from patients with depression, where good tolerability of vilazodone was reported (Shi et al., 2016). More trials will be needed to further elucidate the efficacy of vilazodone in anxious (sub-) populations. As well as showing therapeutic effects in GAD, vilazodone treatment demonstrated greater improvement in anxiety measures than placebo treatment in a randomised controlled study for adult separation anxiety (Schneier et al., 2017) and in generalised SAD (Careri, Draine, Hanover, & Liebowitz, 2015). In contrast, symptoms of PTSD and comorbid depression have not been found to be improved by vilazodone (Ramaswamy et al., 2017).

5.1.2. AVN-101

AVN-101 (2,8-dimethyl-5-penethyl-2,3,4,5-tetrahydro-1 h-pyrido [4,3-*B*]indole hydrochloride), a close structural analogue of the antihistamine latrepirdine, is another multi-modal antagonist, showing highest binding affinity to the 5-HT_7, the histaminergic H1 and the adrenergic α2B receptors, and high affinity to the 5-HT_6, 5-HT_{2A} and 5-HT_{2C} receptors as well as to the adrenergic α_{1B}, α_{2A}, and α_{2C} receptors. It is in the developmental pipeline of Avineuro for GAD. Although it has been primarily tested for Alzheimer's disease, preclinical evidence of anxiolytic and antidepressant properties has stimulated further investigation for its use in GAD and major depression as well as for schizophrenia and multiple sclerosis (Ivachtchenko, Lavrovsky, & Okun, 2016). A Phase 1b trial, completed in 2018, reported that after treatment with AVN-101 for several weeks, the occurrence of adverse events was low and that it was well tolerated in a wide range of doses. Avineuro planned Phase 2 clinical trials for the treatment of GAD, but as of April 2019 there seems to be no further information on this issue (www.avineuro.com).

5.1.3. Brexpiprazole

The atypical antipsychotic brexpiprazole is an antagonist at the 5-HT_{2A}, 5-HT_{2B} and 5-HT_7 receptors, a partial agonist at the 5-HT_{1A} as well as dopamine D_2 and D_3 receptors and has antagonistic properties at the α_1-adrenoceptor, the α_2-adrenreoceptor and the histaminergic H_1 receptor (Maeda et al., 2014). Furthermore, although brexpiprazole exerts only low affinity to the D_1 receptor, it has been shown to facilitate glutamatergic transmission via D_1 receptor dependent mechanisms in the mPFC that could also be important for its anxiety-modulating effects (Bjorkholm, Marcus, Konradsson-Geuken, Jardemark, & Svensson, 2017). It received its first global approval for the treatment of schizophrenia and as an adjunct to established pharmacotherapeutic treatment of major depression in 2015. Further clinical trials are aimed at advancing the use of brexpiprazole as monotherapy and/or as an adjunct for the treatment of additional indications, including agitation, sleep disorders and PTSD, among others. While a Phase 3 study evaluating the efficacy of brexpiprazole as adjunctive treatment to paroxetine or sertraline for PTSD symptoms (NCT01987960) was terminated due to problems with patient eligibility, the safety, efficacy and tolerability of brexpiprazole (as compared with a placebo) as monotherapy or in combination therapy (sertraline) had been assessed in adults with PTSD (NCT03033069) in a Phase 2 study that was completed at the beginning of 2019. Data are not yet available.

5.1.4. Cyclobenzaprine VLD (TNX-102)

Cyclobenzaprine is an antagonist at 5-HT_{2A}, α_1 and H_1 receptors (Daugherty, Sullivan, Gershell, & Lederman, 2015) and was discovered by Vela Pharmaceuticals. The sublingual formulation of very low doses of cyclobenzaprine, also known as *VLD*-cyclobenzaprine, Tonmya® and TNX-102 (sublingual), allows rapid absorption, and is aimed at long-term use with a low risk of severe adverse events that are present with high doses. Cyclobenzaprine is proposed to improve sleep quality via its blockade of 5-HT_{2A} and H_1 receptors (Krystal, Richelson, & Roth, 2013; Monti, 2011), and to reduce trauma-related nightmares and sleep disturbance via blockade of α1-adrenoceptors (Hendrickson & Raskind, 2016). While the investigation of another altered release formulation of cyclobenzaprine, TNX-105, was discontinued, the fast therapeutic onset of Tonmya® is believed to be beneficial for bedtime

treatment of PTSD when sleep is disturbed and nightmares are present. In support of this, Tonmya® reduced the symptoms of PTSD in two randomised, placebo-controlled Phase 2 studies (NCT02277704, NCT02421679). In comparison with a placebo, it also improved sustained remission rates at 12 weeks of treatment when given at bedtime to treat military-related PTSD. Two Phase 3 studies (NCT03062540, NCT03110575) were prematurely terminated after observing similar drug and placebo effects and, thus, the FDA rescinded its breakthrough therapy designations, i.e. fast-track through Phase 3 of clinical trials (Brennan, 2019). However, in a retrospective analysis it was revealed that Tonmya® exerted clinically significant effects only in that subgroup of PTSD patients in whom the trauma had been experienced within nine years prior to study participation, but no longer than that (Sullivan et al., 2018). A new Phase 3 trial, with an improved study design, named the RECOVERY trial, has just started end of February 2019.

5.1.5. Gepirone ER (Travivo®)

The azapirone gepirone is a full 5-HT_{1A} receptor agonist at raphe 5-HT_{1A} autoreceptors and a partial agonist at postsynaptic 5-HT_{1A} receptors. As compared with buspirone, gepirone has greater efficacy in activating the 5-HT_{1A} receptor with negligible affinity for the D_2 receptor. It is an old drug whose therapeutic application was limited by its short half-life. Travivo®, by Fabre-Kramer Pharmaceuticals, is the extended-release (ER) formulation of gepirone reducing fluctuations in plasma drug concentrations and the incidence of adverse events that were associated with high peak plasma concentrations (Robinson, Sitsen, & Gibertini, 2003). It is currently under a new drug application review by the FDA for the treatment of major depression after having been rejected several times. In a retrospective subgroup analysis gepirone ER was found to reduce clinical scores of somatic and psychic anxiety in patients with depression and anxious depression (Alpert, Franznick, Hollander, & Fava, 2004). This evidence is supported by previous studies showing that the immediate release formulation of gepirone was able to improve anxiety ratings as compared with placebo with similar efficacy to the comparator diazepam. According to information from the homepage, gepirone ER is intended to be studied in Phase 3 trials. Another 5-HT_{1A} receptor partial agonist developed by Fabre-Kramer Pharmaceuticals is FKW00GA that also exerts 5-HT_{2A} receptor antagonistic properties. Information is only available from their homepage. So far, FKW00GA has been shown to be safe and well tolerated and there is some evidence of efficacy in patients with GAD as assessed in several Phase 2 clinical trials. According to Fabre-Kramer Pharmaceuticals the protocol for Phase 3 trials of the existing formulation was submitted to the FDA although new ER formulations of FKW00GA are currently developed that might be more beneficial for patients in terms of compliance and side effect profile (Fabre-Kramer, 2019).

5.1.6. Compounds with potential anxiolytic properties on hold/discontinued for drug development in anxiety

Vortioxetine

The antidepressant vortioxetine, developed by Lundbeck and Takeda and approved in 2013, is a 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} receptor partial agonist, a 5-HT_{1A} receptor agonist and an inhibitor of the 5-HT transporter (Bang-Andersen et al., 2011) with a good tolerability and long-term safety profile and no evidence of sexual dysfunction as a side effect. Although Takeda decided to discontinue its development for the treatment of GAD in the USA and other countries in 2015 (Takeda, 2016), a recent meta-analysis provides some support for the potential of vortioxetine for the treatment of anxiety (Yee, Ng, & Seng, 2018), whereby it seems to be more efficient in lowering relapse rate and improving quality of life in adults integrated into the working world or in education than in non-engaged subjects (Christensen, Loft, Florea, & McIntyre, 2017). However, this was not confirmed in the most recent network meta-analysis (Slee et al., 2019). In addition to being of interest for GAD treatment, vortioxetine was shown to decrease the number of panic attacks and to moderately improve the quality of life of patients with PD in an open-label trial with flexible doses (Shah & Northcutt, 2018). These results suggest that vortioxetine could be beneficial for some groups of anxiety patients, but this needs to be further evaluated in long-term placebo-controlled studies and/or in post-market surveys of patients with depression.

Agomelatine

Likewise, the stable synthetic analogue of the pineal neurohormone melatonin, agomelatine, developed by Servier, has been approved for the treatment of major depressive disorder in Europe since 2009, and was shown to have anxiolytic properties (Stein et al., 2014). Agomelatine has a unique mechanism of action (Levitan, Papelbaum, & Nardi, 2015) as it is an agonist at the G-protein coupled melatonin MT_1 and MT_2 receptors and an antagonist at the 5-HT_{2C} and 5-HT_{2B} receptors with very low binding affinity to most other monoaminergic, GABAergic and glutamatergic receptors as well as to potassium and calcium channels (Millan et al., 2003). Melatonin regulates circadian rhythms via action in the suprachiasmatic nucleus of the hypothalamus; but MT_1 and MT_2 receptors are also expressed in areas such as the prefrontal cortex (PFC), the hippocampus, the thalamus and the striatum. 5-HT_{2C} receptor blockade in the frontal cortex disinhibits/increases noradrenaline and dopamine release. Its anxiolytic effect seems to be a result of the synergistic action of this action, antagonising 5-HT_{2C} receptors in subcortical areas including hippocampus and the MT receptor stimulation enhancing neurogenesis and reducing stress-induced glutamate release (Levitan et al., 2015; Tardito, Molteni, Popoli, & Racagni, 2012). In GAD patients, agomelatine has been shown to exert efficacy superior to placebo and comparable to the active comparator escitalopram, though with overall better tolerability, and evidence of preventing anxiety relapse over 6 months in one study [e.g. (Stein, Ahokas, Albarran, Olivier, & Allgulander, 2012; Stein et al., 2018); for review, see (Buoli, Grassi, Serati, & Altamura, 2017; Slee et al., 2019)]. Although the further development of agomelatine for the treatment of GAD is on hold due to a strategic decision by Servier, the evidence of clinical efficacy and the relatively good tolerability of agomelatine in GAD patients (Slee et al., 2019) would call for its further investigation in other anxiety disorders. Since agomelatine has been shown to positively affect sleep-related measures including REM and slow wave sleep and the quality of sleep (Buoli et al., 2017; Guardiola-Lemaitre et al., 2014; Levitan et al., 2015), it is likely to be particularly useful for anxiety patient populations with sleep-related symptoms including also PTSD and OCD (De Berardis et al., 2015).

5.2. GABA system

GABA is the major inhibitory neurotransmitter in the brain. It is synthesised from glutamate by glutamate decarboxylase, released from vesicles and removed from the synapse by reuptake into the nerve terminals or into glial cells. GABA activates two main types of receptors present on postsynaptic, presynaptic and/or extrasynaptic sites. The GABA-A receptor is a ligand-gated ion channel mediating the fast inhibitory actions of GABA by opening the channel pore and prolonging chloride influx to hyperpolarise the cell membrane. The high structural diversity of the GABA-A receptors (see below) and their differential expression in brain circuits and subcellular compartments determine the highly complex and precise inhibitory control of brain circuits important in anxiety (Engin, Benham, & Rudolph, 2018). The metabotropic GABA-B receptors are coupled to inhibitory Gi proteins that produce slow and prolonged inhibition by affecting downstream potassium channels or calcium channels. Animal and human studies have established the critical role of both the GABA-A and the GABA-B receptors in the processing of anxiety, as well as in the pathogenesis and pathology of anxiety disorders (Bandelow et al., 2016; Engin et al., 2018; Nuss, 2015; Pizzo, O'Leary, & Cryan, 2018).

5.2.1. Benzodiazepines

BDZs, which have been in clinical use for decades, not only exhibit rapid anxiolytic effects, but also have sedative, amnestic, anticonvulsant, muscle relaxant and addictive properties (Coric et al., 2005; Engin et al., 2018). The key neuronal circuits and brain areas mediating the anxiolytic effects of BDZs are still not entirely clear, although the limbic system, and the amygdala in particular, has been revealed as a central component (Engin et al., 2018; Griessner et al., 2018). They act as positive allosteric modulators (PAMs) on compatible GABA-A receptors and thus increase GABA-induced chloride conductance and inhibitory postsynaptic potentials (Olsen & Sieghart, 2009). The BDZ binding site is located between the α and γ subunits of the heteropentameric receptors (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, θ, π). While the γ-subunit is important for the binding of BDZs, the α-subunit seems to be important for the diverse beneficial and adverse pharmacological effects of BDZs. A logical rational design strategy to develop more selective BDZ anxiolytics was to identify and target those GABA-A receptor subunits which mediate anxiolytic but not sedative, muscle relaxant or tolerance/dependence-eliciting actions. The contributions of the different α-subunits to the desired therapeutic effects have been evaluated in animals in depth [for review, see (Cheng, Wallace, Ponteri, & Tuli, 2018; Engin et al., 2018)] and have revealed that mainly α_2- and/or α_3-, but also to some extent α_5-containing GABA-A receptors promote the desired anxiolysis. It has been shown that the potency of BDZ may play a role in tolerance development, as full agonists produce more tolerance than partial agonists (Cheng et al., 2018). It is thus proposed that α_2 and α_3 subtype partial agonists with α_1 dormancy may cause little sedation and amnesia in parallel with no or low abuse potential or tolerance building. In line with this idea, several compounds, including L-838,417, imidazenil, TPA123, TPA023, ocinaplon and MRK-409, have demonstrated anxiolytic effects in rodents and/or primates, with reduced or no sedative effects. In healthy humans, only TPA023 with α1 antagonistic properties, but not MRK-409 with weak α1 partial agonistic effects, causes sedation-free anxiolysis (de Haas et al., 2007), as well as in patients with GAD as shown in Phase 2 trials (Atack, 2009). These are important findings which suggest that any remaining agonistic efficacy at the α_1 subtype is undesirable in the development of non-sedative BDZ anxiolytics. Consequently, all ongoing clinical trials (Phase 1–2) with GABA-A receptor agonists or modulators with any potency at the α1 subunit, including pagoclone (Sanofi), CP-409092 (Pfizer), MK-0343 (Merck) AZD-6280 and AZD-7325 (AstraZeneca), were discontinued (Mandrioli & Mercolini, 2015) while the clinical development of TPA-023 was stopped due to preclinical toxicity in long-term dosing studies (Atack, 2009). In 2017 the Phase 2 evaluation of the latest $\alpha_2/\alpha_3/\alpha_5$-subtype selective GABA-A receptor PAM PF 6372865 for the treatment of GAD was terminated as part of a general strategic decision by Pfizer to cease the research and early stage development activities in the field of neuroscience. Currently there are no subtype-selective GABA-A receptor ligands in clinical trials for anxiety disorders (Table 2). Nevertheless, the strategy of subtype-selective BDZ is still of particular interest for the development of compounds eliciting fast relief of anxiety symptoms and lacking unwanted effects such as sedation or dependence. The preclinical research for such ligands is still ongoing (Prevot et al., 2019) in parallel with the identification of novel interesting subunit-specific target sites at the GABA-A receptor such as the α_6 subunit (Gonda et al., 2019).

5.2.2. Neurosteroids

An attractive alternative approach to refine the GABA-A receptor target is represented by neuroactive steroids that bind to the α-intrasubunit, the β-intrasubunit and the βα-intersubunit sites of the GABA-A receptors (with preference to those expressing δ-subunits) that are distinct from those targeted by BDZs and either modulate or directly activate the receptor (Chen et al., 2019; Poisbeau, Gazzo, & Calvel, 2018). Ligands targeting the translocator protein (TSPO), which promotes the endogenous neurosteroidogenesis by supplying cholesterol to the cytochrome P450 enzyme for conversion into pregnenolone, have received particular interest. For example, etifoxine is a long known drug developed by Hoechst in the 1960s. Although it is not approved by the FDA or EMA, it is marketed in approximately 40 countries including France (approved in 1979) for the treatment of anxiety disorders (Poisbeau et al., 2018). Interestingly, etifoxine exerts its anxiolytic effects without sedation and ataxia via two mechanisms of action at the GABA-A receptor: a direct action as a PAM binding to the β_2 and β_3 subunits of the GABA-A receptor preferentially potentiating α2β3γ2S and α3β3γ2S containing GABA-A receptors, and indirectly by stimulating the biosynthesis of neurosteroids including 17-hydroxypregnenolone that potentiate GABA-A receptor activity (Mattei et al., 2019; Nuss, Ferreri, & Bourin, 2019). Although its use is limited by reports of the occurrence of adverse effects such cutaneous reactions, hepatotoxicity, colitis and metrorrhagia in a substantial number of people (Cottin et al., 2016), the therapeutic profile of this drug is interesting for drug development. The principal concept that synthetic and/or natural neurosteroids may be considered as anxiety treatment is supported by the increasing evidence of altered neurosteroid homeostasis in anxiety and related disorders (Aspesi & Pinna, 2019). Furthermore, it has been proposed that the anxiolytic actions of SSRIs such as fluoxetine are due to their ability to increase neurosteroid levels in the brain of rodents as well as in the CSF and plasma of depressed patients (Longone et al., 2011). Currently, a randomised clinical Phase 2 trial is evaluating the potential of the neurosteroid precursor pregnenolone in improving symptoms of PTSD in Iraq/Afghanistan-era Veterans. Another Phase 2 trial is studying whether pregnenolone is able to enhance EBT in OCD (Table 2) although a pilot interim report is not showing much promise yet (Kellner, Nowack, Wortmann, Yassouridis, & Wiedemann, 2016).

A synthetic neurosteroid that deserves specific attention is aloradine (4-androstadienol, 4,16-androstadien-3β-ol) which is an odourless isomer of the endogenous neurosteroid pheromone androstadienol. Aloradine lacks affinity for the steroid hormone receptors, but binds with high affinity to the nasal chemosensory receptors in humans, a group of G-protein coupled receptors that mediate the detection of pheromone signals. This transmission pathway is neuronally connected to basal forebrain areas rapidly affecting neuronal activity in the amygdala, the hypothalamus and the PFC, as well as autonomic and behavioural responses (Liebowitz et al., 2016). Aloradine does not bind to monoaminergic, glutamatergic, peptidergic, opioid, glucocorticoid or sex-hormone receptors (Liebowitz et al., 2016) and it is not clear whether it targets the GABA-A receptor. Since, however, androstenol, a product of its endogenous isomer androstadienol, is a PAM at the GABA-A receptor by binding to the neurosteroid binding site and has been shown to reduce anxiety-related behaviour in animals (Kaminski, Marini, Ortinski, Vicini, & Rogawski, 2006), it may be speculated that the GABA-A receptor also represents either a direct or indirect mechanism of anxiolytic action of aloradine.

Aloradine is under development as a nasal spray (PH94B) by Pherin Pharmaceuticals for the acute treatment of SAD. Liebowitz and co-workers reported the results of a randomised clinical trial demonstrating that 15 min after its intranasal application, aloradine already reduced performance anxiety and social interaction anxiety to a greater extent than a placebo in a provoked public-speaking challenge in female patients diagnosed with generalised SAD (Liebowitz et al., 2014). This evidence of efficacy in the clinical setting is now supported by first results from a randomised clinical Phase 3 pilot feasibility study in men and women with SAD. It is reported that in an everyday life setting aloradine rapidly improves symptoms of social anxiety in participants who were allowed to self-administer aloradine nasal spray 15 min prior to an upcoming feared situation (Liebowitz et al., 2016). Given that aloradine, so far, has shown a side-effect profile similar to placebo, the follow-up multi-centre Phase 3 trial launched by VistaGen in 2019 will be of considerable interest.

6. Novel anxiolytic compounds acting on alternative pharmacological target systems

6.1. Glutamate system

Glutamate is the principal excitatory neurotransmitter in the brain, and it exerts its various biological functions via the fast-acting ionotropic *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) and kainate receptors, as well as the mGluR1–8 (Reiner & Levitz, 2018). The glutamate system serves as an important mediator of neuroplasticity-dependent learning and memory formation, including fear extinction (Section 8). There is long-standing research interest in developing anxiolytic agents that act through glutamatergic mechanisms. Despite these efforts, we still know relatively little about the glutamate system in the pathogenesis and perpetuation of anxiety disorders (Bandelow et al., 2016). Stress that is considered a risk factor in the development of anxiety disorders alters levels of glutamate in rodents, and, indeed, patients with an anxiety disorder display abnormal levels of glutamate and glutamate receptors (Krystal et al., 2017). It has been proposed that anxiety disorders may be the result of the dysbalanced neurotransmission of glutamate and GABA, and that associated neuroplastic changes are the basis for the neuroplasticity model of anxiety disorders (Cocks, Carta, Arias-Carrion, & Nardi, 2016). There is strong preclinical evidence that drugs reducing glutamatergic neurotransmission cause fast antidepressant and anxiolytic effects in animals and humans (Williams & Sanacora, 2015). While some promising examples are given below, testing results of the mGluR5 negative allosteric modulator RHG-618 or of the selective mGluR2 PAM JNJ-40411813 (=ADX-71149) for the indication depression with anxiety and/or anxiety disorders in Phase 1 and 2 clinical trials were not sufficiently convincing to suggest further development. We here focus on interesting anxiolytic agents that act through glutamatergic mechanisms, but that are different to those used in conjunction with EBT, which are discussed in Section 8.

6.1.1. Ketamine

Ketamine can be categorised as a dissociative anaesthetic, hallucinogenic and psychotomimetic drug with strong analgesic properties. It is a mixture of (*S*)- and (*R*)-ketamine that acts as an uncompetitive (though mostly termed non-competitive) NMDA receptor antagonist by binding deep inside the open channel, with the R-enantiomer displaying lower binding affinity than the S-enantiomer. At subanaesthetic doses ketamine reaches brain concentrations that allow modulation of specific subpopulations of NMDA receptors (Dravid et al., 2007, Kotermanski, Wood, & Johnson, 2009). This fact, however, seems to be critical as anaesthetic doses of ketamine do not produce antidepressant effects (Zorumski, Izumi, & Mennerick, 2016). The mechanisms of action of ketamine have been intensively studied in the last two decades, in particular in relation to its fast and sustained antidepressant effects, revealing complex, direct and indirect effects upon NMDA receptor blockade. Although still not entirely clarified in detail, some of these proposed antidepressant mechanisms may be important for ketamine's anxiolytic effects (see also Fig. 3): First, in the mPFC and hippocampus blockade of GluN1/GluN2C containing NMDA receptors located preferentially on GABAergic interneurons by ketamine causes disinhibition and (persistently) enhances AMPA receptor-mediated excitatory neurotransmission. As a result, brain derived neurotrophic factor (BDNF) signalling via the TrkB (tropomyosin receptor kinase B) receptor and further downstream the mammalian target of rapamycin (mTOR) complex are activated. Second, BDNF signalling is also enhanced by inhibition of the eukaryotic elongation factor 2 via blockade of spontaneously activated Glu2B-containing NMDA receptors on principal neurons in the cortex and hippocampus. Third, the blockade of extrasynaptic NMDA receptors disinhibits the mTOR complex signalling. Forth, there is recent evidence that ketamine also causes increased stimulation of postsynaptic 5-HT1A receptors in the mPFC activating the phosphoinositide-3 kinase/Akt/mTOR complex pathway further downstream (Fukumoto, Iijima, Funakoshi, & Chaki, 2018). Both BDNF and mTOR complex appear to be the key effectors for rapidly enhancing synaptic connectivity and increasing dendritic spines (Castren & Hen, 2013; Fortress, Smith, & Pang, 2018) and are proposed to underlie the persistent antidepressant effects of ketamine. Furthermore, the long-lasting effects of ketamine could be also mediated via its active metabolite hydroxynorketamine (Kadriu et al., 2019; Zorumski et al., 2016).

The idea that subanaesthetic doses of ketamine may be helpful in the treatment of anxiety disorder has arisen from animal studies and from off-label use in patients with treatment-resistant anxious and non-anxious depression (Gerhard, Wohleb, & Duman, 2016; Ionescu et al., 2014; Salloum et al., 2019). In a double-blind, randomised clinical trial a single dose of intravenous ketamine has been shown to reduce core symptom severity in patients with chronic PTSD 24 h post treatment to the same extent as the active BDZ comparator midazolam (Feder et al., 2014). Other retrospective or case-report studies have supported the potential utility of subanaesthetic doses of ketamine in treating PTSD (Abdallah, Averill, & Krystal, 2015; Hartberg, Garrett-Walcott, & De Gioannis, 2018). Indeed, several clinical trials are currently ongoing investigating the efficacy of (repeated) doses of ketamine in reducing the symptoms of PTSD (Table 2). An interesting mechanistic aspect for future investigation is whether ketamine acts via interference with fear-memory reconsolidation in PTSD (McGowan et al., 2017; Veen, Jacobs, Philippens, & Vermetten, 2018), since one would argue that extinction memory building mechanisms would be impaired by NMDA receptor antagonism (Section 8). Ketamine was also shown to reduce anxiety symptoms in adults with treatment-refractory GAD (Glue et al., 2017) and with SAD, with reported increased social engagement on subsequent days (Taylor et al., 2018). Mixed results were reported in patients with OCD (Murrough, Yaqubi, Sayed, & Charney, 2015): a single ketamine infusion (0.5 mg/kg) caused fast and prolonged (for at least a week) clinically relevant relief of OCD symptoms (Rodriguez et al., 2013), while a negative outcome was reported in an open trial (Bloch et al., 2012). A Phase 2 study is currently aiming to gain insight into how ketamine causes these rapid improvements of OCD symptoms by investigating central levels of glutamate and GABA (NCT02624596, Table 2). Although ketamine treatment was generally well tolerated in these clinical trials and S-ketamine (esketamine) has just been approved for the treatment of treatment-resistant depression by the FDA in form of a nasal spray (FDA, 2019; The Scientist, 2019), its safety has to be carefully evaluated when given at higher doses over a longer period of time as it elicits euphoric and dissociative effects and may increase the incidence of cardiovascular effects, hepatotoxicity and ulcerative cystitis (Cohen et al., 2018). For the moment it is recommended to be applied at the clinical setting where it can be controlled. While mostly single doses of ketamine have been tested so far, first information on the efficacy, safety and durability of repeated ketamine infusions has recently been reported for treatment-refractory GAD (Glue et al., 2018) and PTSD comorbid with treatment-resistant depression (Albott et al., 2018). Similar to ketamine, the NMDA receptor antagonist AZD6765, or lanicemine (AstraZeneca), a blocking molecule that is trapped inside the NMDA channel pore, exerts rapid, but short-lived, antidepressant effects in clinical trials without evidence of eliciting psychotomimetic effects (Zarate Jr. et al., 2013). A now registered Phase 1b study is aimed at examining the safety and efficacy of parenterally-administered lanicemine in a parallel-arm, randomised, double-blind, placebo-controlled trial in patients with significant PTSD symptoms and elevated fear-potentiated startle (NCT03166501).

6.1.2. Xenon gas (NBTX-001)

The active constituent of NBTX-001 developed by Nobilis Therapeutics is the inert noble gas xenon, an approved anaesthetic with the advantage of producing no metabolites (NobilisTherapeutics, 2019). Pharmacologically, it is a multi-target agent reducing excitatory neurotransmission by inhibition of the NMDA receptor (by competing with

the co-agonist glycine at aromatic residues of the glycine binding site), AMPA-, nicotinic acetylcholine, 5-HT_3 receptors and HCN (hyperpolarization-activated cyclic nucleotide–gated) channels and causing neuronal hyperpolarization by activating potassium channels (Zhou, Liu, & Chen, 2012). Furthermore, treatment with xenon has been shown to decrease pro-inflammatory cytokine levels, including TNFα and IL1β, and to upregulate growth factors such as BDNF [for details and references, see (Dobrovolsky, Ichim, Ma, Kesari, & Bogin, 2017)]. In animals, inhalation of sub-anaesthetic concentrations of xenon (25% for 1 h) was shown to reduce fear-related behaviour by impairing fear memory reconsolidation suggesting that xenon inhalation may have potential for therapeutic blocking of trauma memory reconsolidation (Meloni, Gillis, Manoukian, & Kaufman, 2014) (see also Section 8). This idea is supported by preclinical findings showing that xenon reduces NMDA-induced synaptic currents and neuronal plasticity in brain areas involved in fear learning and memory processes including the amygdala and hippocampus (Haseneder et al., 2008; Kratzer et al., 2012). In a recently published open-label study involving 80 patients with diagnosed PD, the sub-chronic inhalation of sub-anaesthetic concentrations of a xenon-oxygen mixture immediately and progressively reduced the occurrence of panic attacks as well as of anxiety in general, and this reduction lasted up to 6 months after treatment (Dobrovolsky et al., 2017). These first human data were the basis to file an investigational new drug application with the FDA for a phase 2b/3 trial to further study the efficacy of xenon-assisted treatments for patients with PTSD (NCT03635827), but patient recruitment has not started yet.

6.2. Endocannabinoid system

The eCB system comprises two endogenous ligands, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), their degrading enzymes, hydrolase fatty acid amide hydrolyse (FAAH), cyclooxygenase 2 (COX-2) and monoacylglycerol lipase (MAG-L). Receptors include the cannabinoid 1 receptor (CB1), the cannabinoid 2 receptor (CB2) and the presynaptic TRP1 (transient receptor potential vanilloid receptor) [for review, see (Patel, Hill, Cheer, Wotjak, & Holmes, 2017)]. CB1 is densely expressed in brain areas relevant to anxiety and is the main eCB receptor to which AEA and 2-AG bind, mediating the many behavioural and brain functions of eCB (Patel et al., 2017). The eCB system has been shown to modulate fear, anxiety and stress-related neuronal activity. Enhanced eCB signalling – for example, induced by blocking the serine hydrolase enzyme FAAH – reduces stress and anxiety responses and promotes fear-extinction learning (Gunduz-Cinar, Hill, McEwen, & Holmes, 2013; Lisboa et al., 2019; Mayo et al., 2019; Patel et al., 2017). Hence, the complexity of the eCB system allows pharmacological modulation at different sites for potential treatment of anxiety disorders (Griebel & Holmes, 2013; Patel et al., 2017).

6.2.1. Cannabis

Cannabis has been used for traditional and medicinal purposes in many cultures dating as far back as 2700 BCE. The plant is comprised of a variety of over 100 components, including the two major phytocannabinoids, Δ9-tetra-hydrocannabinol (THC) and cannabidiol (CBD). While THC is a partial CB_1 receptor agonist and exerts its psychoactive and hypnotic effects via this receptor, CBD has low affinity for both the CB_1 and the CB_2 receptor. It acts as negative allosteric modulator at the CB_1 receptor - explaining the lack of CB1-associated psychotropic effects - and as a partial agonist at the 5HT1A receptor which seem to be important for its anxiolytic and anti-panic effects. CBD furthermore increases eCB levels, in particular of AEA (Crippa, Guimaraes, Campos, & Zuardi, 2018; Soares & Campos, 2017) and has been shown to modulate the activity in anxiety-relevant brain areas including the mPFC, hippocampus and amygdala [see Fig. 3; (Crippa et al., 2018)]. Natural, plant-based medical preparations (e.g. marijuana, tincture) and synthetic cannabinoids are already used for diverse diseases, including multiple sclerosis, chemotherapy-induced nausea, chronic pain, neuropathic pain and chemotherapy-induced nausea (Turna, Patterson, & Van Ameringen, 2017). Self-medication with cannabis seems to be frequent, however systematic studies assessing effects in anxiety are lacking. Extending evidence from anecdotal self-reports of (chronic) cannabis users, several studies in healthy individuals claim acute anxiolytic, stress-reducing and relaxing effects of cannabis (Turna et al., 2017). Cannabis use or cannabis use disorder is positively associated with anxiety in the general population, likely used as self-medication (Kedzior & Laeber, 2014), and is particularly common in patients with PTSD (Gentes et al., 2016). However, cannabis use itself can increase the risk for the onset of anxiety disorders, with greater symptom severity and with poorer treatment outcome [(Grunberg, Cordova, Bidwell, & Ito, 2015; Mammen et al., 2018; Zvolensky et al., 2006), but see (Feingold, Rehm, Factor, Redler, & Lev-Ran, 2018)].

The pharmacological potential of cannabis constituents for treating neuropsychiatric conditions, including major depressive disorder, bipolar disorder, trichotillomania and Tourette's syndrome, as well as anxiety disorders, is currently under intense investigation (Turna et al., 2017; Whiting et al., 2015). Only a few clinical studies have investigated the effects of cannabinoids in patients with diagnosed anxiety disorders. CBD, which has anticonvulsant, antipsychotic and muscle-relaxant properties, but lacks the psychoactive and 'high-inducing' effects of THC, attenuates anxiety measures and autonomic arousal as well as the activation of the amygdala and the anterior cingulate cortex in response to fearful faces in healthy volunteers (Rabinak & Phan, 2014). In treatment-naïve patients with generalised SAD a single dose of CBD was found to significantly reduce anxiety and associated anticipatory alert, as well as discomfort provoked during a public-speaking test (Bergamaschi et al., 2011; Crippa et al., 2011). Recently, a multi-centre Phase 3 study was started aimed at evaluating the efficacy of CBD (200-800 mg/day) in treating symptoms of GAD, SAD, PD or agoraphobia in adults over eight weeks of treatment. In addition, potential changes in biological markers for inflammation will be assessed (NCT03549819). Furthermore, the synthetic CB_1 and CB_2 receptor agonist and THC analogue nabilone, when used as adjunctive to other medications and/or psychotherapy, was effective in reducing nightmares and improving sleep quality in PTSD patients. These effects were coming along with a global clinical improvement and improved general well-being (Cameron, Watson, & Robinson, 2014; Jetly, Heber, Fraser, & Boisvert, 2015). The first clinical trials evaluating the effects of nabilone (Phase 1) or marijuana (Phase 2) in OCD are currently ongoing (Table 2). The Phase 2 study (NCT03274440) investigates different THC:CBD ratios (high THC/low CBD vs. low THC/high CBD), as THC and CBD have been shown to elicit often opposite pharmacological effects (Bhattacharyya et al., 2010). This is an important question as low doses of THC are anxiolytic and high doses of THC are arousing and anxiogenic, and CBD is able to block the anxiogenic effects of THC (Kamal, Kamal, & Lantela, 2018).

6.2.2. FAAH inhibitors

As mentioned above, the membrane-bound enzyme FAAH hydrolyses the endogenous cannabinoid AEA. AEA levels have been shown to be reduced in PTSD patients (Hill et al., 2013; Neumeister et al., 2013) and depressed patients with high anxiety scores (Hill, Miller, Carrier, Gorzalka, & Hillard, 2009; Hill, Miller, Ho, Gorzalka, & Hillard, 2008). Moreover, a destabilising polymorphism in the FAAH gene causes increased AEA levels and is associated with lower indices of trait anxiety as well as with enhanced cortico-amygdala connectivity and reduced amygdala activation in response to threat stimuli (Patel et al., 2017). In rodent studies, both the pharmacological and the genetic inhibition of FAAH cause anxiolytic-like effects, in particular under highly aversive or stressful conditions (Patel et al., 2017). The development of the FAAH inhibitor SSR-411298 by Sanofi for the treatment of major depression and anxiety was discontinued after the disappointing outcome of a Phase 2b trial in elderly patients (Mandrioli & Mercolini, 2015). The selective FAAH inhibitor JNJ-42165279, developed by Janssen Research &

Development, is currently undergoing a Phase 2 trial for the indication major depressive disorder with anxious distress (NCT02498392), while a Phase 2 randomised clinical trial investigating its efficacy in patients with SAD (NCT02432703) was completed in October 2018, though no results are available yet. Although JNJ-42165279 appeared to be safe among the participants, the studies were temporarily suspended in 2016 for precautionary reasons as severe adverse effects (including the death of one volunteer) had been reported with another FAAH inhibitor, BIA 10–2474, developed for pain relief. During the period of its suspension, it was revealed that these problems were due to off-target effects of this agent that led to alterations in lipid networks in the cortex – effects which were not observed in more specific FAAH inhibitors (van Esbroeck et al., 2017).

6.2.3. Other targets in the eCB system

Since 2-AG has been shown to exert anxiolytic-like effects in preclinical studies (Patel et al., 2017), it is possible that modulators of the activity of its degrading enzymes MAG-L and COX-2 could also represent potential anxiolytic drug targets. In patients with PTSD or depression 2-AG plasma levels have been found to be lower than in healthy controls (Hauer et al., 2013), and in mice lacking the 2-AG synthesising enzyme diacylglycerol lipase anxiety-related behaviour is enhanced (Jenniches et al., 2016; Shonesy et al., 2014). Increasing central 2-AG concentrations by inhibiting MAG-L, its main degrading enzyme, reduces anxiety-related behaviours in rodents (Patel et al., 2017). An alternative target in the eCB system may be COX-2, which is responsible for the degradation of both eCBs. When COX-2 is inhibited, AEA and, to a lesser extent, 2-AG accumulate in the brain (Hermanson et al., 2013). Substrate selective COX-2 inhibitors have demonstrated robust anxiolytic effects in rodents (Gamble-George et al., 2016; Patel et al., 2017). An additional benefit of COX-2 inhibitors could be the simultaneous synthesis inhibition of pro-inflammatory cytokines/chemokines, which are suggested to be associated with heightened anxiety (Felger, 2018). However, probably due to still limited preclinical evidence, there is no clinical study investigating specifically the anxiolytic effect of registered COX-2 inhibitors (Table 2), although the two COX-2 inhibitors Lumiracoxib and Celecoxib are approved as anti-inflammatory substances.

6.3. Neuropeptide systems

Diverse neuropeptides are expressed and released in regions of anxiety/fear neurocircuitries, often together with classical transmitters (Hökfelt et al., 2018). Some neuropeptides have been shown to functionally affect anxiety-related behaviour in animals and thus represent interesting candidate target systems for the development of novel anxiolytics. Specifically, neuropeptides such as neuropeptide S (NPS), neuropeptide Y (NPY), oxytocin (OXT) and others can act as natural anxiety-reducing molecules, and therefore mimicking their effect or enhancing their endogenous action would potentially produce anxiolysis with fewer side effects than traditional anxiety medications. Alternatively, the same pharmacological advantage could be achieved by blocking the functions of endogenous anxiogenic neuropeptides such as the stress-related modulators corticotropin releasing hormone (CRH), vasopressin, substance P, cholecystokinin and others with the respective antagonists representing another line of drug development in this field.

6.3.1. Vasopressin system: SRX246

The nonapeptide vasopressin is well known for its roles in hydromineral balance as well as in stress responses as a neuromodulator and via potentiating the stimulatory effect of CRH on adrenocorticotropic hormone secretion. Its central actions are mediated by binding to the two G-protein coupled V_{1A} and V_{1B} receptors which are distributed in many anxiety- and fear-related brain areas including in the lateral septum, cortex and hippocampus, with V_{1A} receptors being the predominant receptor (Landgraf, 2006). Studies in humans showed that the release of vasopressin was significantly correlated with anxiety symptoms in healthy volunteers after anxiogenic drug challenge (Abelson, Le Melledo, & Bichet, 2001). Furthermore, plasma vasopressin levels are elevated in patients with PTSD (de Kloet, Vermetten, Geuze, Wiegant, & Westenberg, 2008) and with OCD (Altemus, Cizza, & Gold, 1992). Thus, it was suggested that normalising vasopressinergic activity via blockade of its receptors may be helpful for treating stress-related mental disorders including anxiety and trauma-related disorders. Indeed, V_{1A} and V_{1B} receptor antagonists have demonstrated anxiolytic and antidepressant effects in preclinical studies (Bleickardt et al., 2009; Hodgson et al., 2014). While the development of V_{1B} receptor antagonists (e.g. SSR149415) was discontinued for the treatment of anxiety disorders because it did not meet the efficacy expectations (Griebel & Holsboer, 2012), the brain-penetrating small-molecule selective V_{1A} receptor antagonist SRX246 (Azevan Pharmaceuticals) decreased aggression, anxiety, depression, fear and stress in male and female adults with intermittent explosive disorder in a multi-centre randomised Phase 2 exploratory study (Azevan, 2016). In a Phase 1 clinical trial, SRX246 demonstrated a good safety profile upon single and repeated ascending dosing (Fabio et al., 2013) and attenuated amygdala activation in response to angry faces (Fig. 3) and vasopressin administration indicating a role of amygdalar V_{1A} receptors in the processing of aversive emotional information (Lee et al., 2013). Thus, SRX246 is considered promising for further clinical development as a treatment for PTSD and GAD as well as anger disorders. These indications are currently under investigation in a Phase 1 trial and a Phase 2 trial (Table 2).

6.3.2. Oxytocin system

The nonapeptide OXT, traditionally known for its role in milk letdown and uterine contraction during labour and often termed the 'love hormone', is also released during stressful situations in brain areas associated with anxiety, fear and stress responses, including the mPFC, the hypothalamus, the hippocampus and the amygdala (Neumann & Slattery, 2016). OXT is proposed to counteract stress-associated responses, including fear (Naja & Aoun, 2017). Via its receptor, a G protein-coupled receptor capable of binding to either Gαi or Gαq proteins, OXT can activate a set of signalling cascades, such as the mitogen-activated protein kinase (MAPK), protein kinase C, phospholipase C, or CamK (Ca^{2+}/calmodulin-dependent protein kinase) pathways, which converge on transcription factors like CREB (cAMP response element-binding protein) or MEF-2 (myocyte enhancer factor-2). The cellular response to OXT includes regulation of neurite outgrowth, cellular viability, and increased survival (Jurek & Neumann, 2018). OXT also interacts with different neurotransmitter and modulator systems, including 5-HT, dopamine, GABAergic and glutamatergic systems (Naja & Aoun, 2017). As a result of these actions OXT treatment decreases amygdala activity in response to negative/fearful emotions (Fig. 3) and increases the activity of cortical and subcortical regions, often in a sex-specific way (Gao et al., 2016). Furthermore, OXT was shown to affect functional coupling of mPFC and amygdala in healthy participants (Dodhia et al., 2014).

Low OXT function has been associated with high anxiety. Furthermore, genetic and epigenetic variations in the OXT receptor gene have been associated with alterations in socio-emotionality and, in part, with increased stress responses (Naja & Aoun, 2017). In animals, OXT has demonstrated anxiolytic, (social) fear-reducing and extinction-facilitating effects (see Section 8) in various established paradigms (Jurek & Neumann, 2018; Naja & Aoun, 2017). Due to the impermeability of the blood-brain barrier for systemically administered neuropeptides, the intranasal route has been proposed as a potential method for OXT delivery into the human brain (Leng & Ludwig, 2016), although the efficacy of such an administration route remains unclear. OXT applied via this route has been shown to exert rapid anxiolysis also in humans – for example, in patients with GAD [for review, see

(Neumann & Slattery, 2016)]. In highly socially anxious individuals intranasal OXT reduces attentional bias for emotional faces to the level of healthy individuals suggesting the potential therapeutic use of this form of OXT in the treatment of social anxiety (Clark-Elford et al., 2014). Along the same lines, OXT preferentially enhances prosocial behaviours in SAD patients (Fang, Treadway, & Hofmann, 2017). Various clinical trials evaluating the therapeutic benefit of OXT in anxiety disorders and PTSD are currently ongoing (Table 2). However, the varying effects of OXT in social and non-social situations need to be further studied before OXT treatment can be recommended as an anxiolytic and/or extinction-enhancing strategy (see Section 8); nevertheless, this system remains a promising target for future drug development.

6.3.3. Orexin system

Another hypothalamic neuropeptide system is orexin (also named hypocretin) comprising of two isoforms, orexin-A and orexin-B. The orexins exert many different physiological functions including arousal/wakefulness, energy homeostasis, reward processing and stress regulation. The physiological actions of the orexins are mediated by two G-protein-coupled receptors, the orexin receptor 1 and the orexin receptor 2 receptor, that mainly activate the phospholipase C/protein kinase C pathway. The orexin receptor 1 and/or orexin receptor 2 receptor are expressed in several brain areas that are engaged during anxiety and fear processing including the hippocampus, amygdala and mPFC (Flores, Saravia, Maldonado, & Berrendero, 2015; Marcus et al., 2001). Activity in the orexin system has been shown to be associated with the maintenance of arousal and its hyperactivity is proposed to represent an important feature of PD. Furthermore, activation of the orexin system has been shown to be involved in the expression and consolidation of fear while it counteracts fear extinction (Flores et al., 2015). These findings have raised interest in the therapeutic potential of substances that antagonise orexin signalling for the treatment of anxiety disorders, in particular for PD, PTSD and phobias (James, Campbell, & Dayas, 2017). The dual orexin receptor antagonist suvorexant, approved for the indication of insomnia by the FDA, is currently investigated for its potential in alleviating sleep disturbances in patients with PTSD in three clinical phase 2 trials (Table 2). Furthermore, in a pilot study it is investigated whether suvorexant affects levels of orexin in people with PD and whether this is associated with decreased panic symptoms in response to a carbon dioxide (CO_2) challenge (Table 2).

6.3.4. Other neuropeptide systems

There are several additional neuropeptide systems that have potential as targets for drug development in anxiety, but for different reasons they are not in clinical development yet, or any longer. However, recently gained knowledge, also including neuropeptide interaction with anxiety mediators, may awaken or rekindle interest in some of these peptides. For example, **NPY** is the most abundant neuropeptide in the brain, acting via at least five different G-protein coupled receptors (Y_1, Y_2, $Y_{4–6}$) (Reichmann & Holzer, 2016). From animal studies it is known that NPY mediates anxiolysis e.g. by inhibiting amygdalar activation and increasing calcineurin-induced synaptic remodelling in the basolateral amygdala (via the Y_1 receptor), counteracting the anxiogenic effect of CRH, reducing noradrenergic activity in the locus coeruleus and inhibiting excitatory neurotransmission in the dorsal periaqueductal grey (Kask et al., 2002; Reichmann & Holzer, 2016). In patients with PTSD low levels of NPY in the cerebrospinal fluid are correlated with the presence of intrusive traumatic memory and heightened amygdala response (Reichmann & Holzer, 2016; Wu et al., 2011). In a recent randomised clinical Phase 1 trial in patients with PTSD, intranasally administrated NPY showed a greater reduction in anxiety symptoms in a dose-dependent manner along with good tolerability than placebo, supporting the push for further studies investigating the efficacy and safety of the repeated administration of NPY in patient cohorts (Sayed et al., 2018).

An unfortunate example of anxiety drug development is represented by **$CRHR_1$ receptor antagonists**. Elaborate preclinical studies showing that the overactivation of $CRHR_1$ by CRH drives the stress system and anxiety-related behaviours, have triggered the development of a number of non-peptidergic, orally available and brain-penetrating CRHR1 antagonists (Holsboer, 2001; Zorrilla & Koob, 2010). In rodents these compounds have mostly been shown to be anxiolytic (Kaffman, White, Wei, Johnson, & Krystal, 2019). However, since monotherapy with $CRHR_1$ receptor antagonists including verucerfont (GSK-561679, NBI-77860), R121919 (NBI-30775) and pexacerfont (BMS-562086) does not exhibit greater efficacy than placebo for the treatment of PTSD (Dunlop et al., 2017), GAD, SAD and major depressive disorder, despite good tolerability of these drugs in all of these clinical trials (Griebel & Holsboer, 2012), it may be that only subpopulations of patients are sensitive to their therapeutic effects that need to be further investigated (Spierling & Zorrilla, 2017). After the latest disappointing clinical trials, verucerfont has disappeared from the product pipeline of Neurocrine Biosciences for PTSD, but remains a treatment for congenital adrenal hyperplasia (https://www.neurocrine.com/pipeline/pipeline-overview/).

Similarly, the **substance P system** has received longstanding interest in anxiety research. In animal studies, substance P modulates anxiety-related behaviour via its three neurokinin receptors. In Phase 2 clinical trials, however, the efficacy of several neurokinin 1, neurokinin 2 and neurokinin 3 receptor antagonists, including vestipitant, orvepitant, saredudant and osanetant, in reducing symptoms in patients with GAD, SAD, PTSD and PD was inconsistent or negative. This resulted in the discontinuation of the substance P programmes of major pharmaceutical companies (Ebner, Sartori, & Singewald, 2009). Nevertheless, the recent finding that there is a positive correlation between neurokinin 1 receptor expression in the amygdala and trait anxiety, could stimulate further research on neurokinin 1 receptor antagonists as potential anxiolytics, at least for specific subpopulations of patients (Hoppe et al., 2018).

Finally, **NPS** is a more recently characterized neuropeptide that exerts anxiolytic and arousal/activity promoting effects, and has been shown to enhance extinction learning- [for recent review, see (Grund & Neumann, 2019)]. The potential of the NPS system as a novel anxiolytic target is supported by studies in humans showing that a polymorphism in the NPS receptor gene, resulting in an amino acid exchange of asparagine to isoleucine (A/T) at position 107 and a more functional variant, is associated with PD and distorted cortico-limbic activity during emotion processing in healthy adults and PD patients, as well as with increased anxiety-sensitivity upon gene-environment interactions. Thus, it is proposed that an overstimulation of NPS-sensitive circuits in A/T SNP carriers may contribute to the development of anxiety- and stress-related disorders [for recent review, see (Grund & Neumann, 2019)]. At the moment it is not clear whether and how the existing rodent data concerning the pronounced anxiolytic effects of NPS can be translated into humans in particular due to lacking information on the exact distribution of NPS and its receptors system in the human brain and the lack of orally bioavailable and blood-brain barrier penetrating NPS receptor agonists (Sartori & Singewald, 2017).

6.4. Voltage-gated ion channels

6.4.1. Riluzole and Troriluzole

Riluzole is approved for the treatment of amyotrophic lateral sclerosis and has shown neuroprotective and anticonvulsant effects. The pharmacodynamic profile of riluzole is complex. It is a voltage-sensitive sodium channel blocker with high affinity for inactivated channels resulting in the inhibition of high-frequency neuronal firing. At higher concentrations, riluzole interacts with other presynaptic voltage-gated ion channels, including calcium and potassium channels. As a proposed main mechanism, riluzole reduces glutamatergic neurotransmission by blocking NMDA receptors, increasing synaptic AMPA

receptor trafficking and the clearance of glutamate via glutamate transporters. Furthermore, stimulation of neurotrophic factor synthesis including the VEGF (vascular endothelial growth factor) and BDNF was observed (Bellingham, 2011). The drug has also been shown to affect GABA-A receptors at high concentrations. In rodents, a single dose of riluzole produces clear anxiolytic effects in a dose-dependent manner (Sugiyama et al., 2012) without evidence of oversedation, amnesia or coordinative problems as seen with BDZs. Riluzole was shown to reduce clinical symptoms in adults with treatment-refractory OCD when used as add-on to existing pharmacotherapy, including SSRIs and antipsychotics (Coric et al., 2005; Pittenger et al., 2015). Interestingly, in an eight-week open-label pilot study in patients with GAD, riluzole caused a reduction in clinician-rated anxiety symptoms as well as in patient-reported anxiety sensitivity (Mathew et al., 2005). Furthermore, it has been shown to improve anxiety symptoms in patients with diagnosed major depressive disorder when given alone or in combination with standard antidepressant treatment (Sanacora, Kendell, Fenton, Coric, & Krystal, 2004), although the newest study was not able to reproduce this effect (Mathew, Gueorguieva, Brandt, Fava, & Sanacora, 2017). An open-label and a randomised clinical trial are currently evaluating the safety and efficacy of oral riluzole either as monotherapy or as augmentation treatment in patients with PTSD (Table 2). This relatively preliminary evidence has convinced authorities to pass a double-blind, placebo-controlled cross-over study evaluating the acute effects of a single sublingual dose of riluzole (BHV-0223 under licence of Biohaven) on anxiety symptoms in subjects with diagnosed SAD in an anxiety-provoking speech task. This treatment is bioequivalent to riluzole tablets, but associated with less pharmacokinetic variability. In August 2018, Biohaven reported that BHV-0223 met the primary endpoint of significantly reducing anxiety in the 21 recruited patients with SAD (www.Biohavenpharma.com). Furthermore, the tripeptide prodrug conjugate of riluzole, troriluzole (or trigriluzole), developed to overcome the limitations of riluzole in terms of bioavailability, safety and dosing, is a substrate for the gut transporters PepT1, resulting in improved bioavailability. On the basis of a favourable safety and tolerability profile, the FDA has approved a Phase2/3 trial to start clinical investigations of troriluzole for the indication OCD (NCT03299166). A year ago, Biohaven Pharmaceutical Holding Company announced that the first patient was enrolled, but no further information is available. Meanwhile, in early 2019 a Phase 3 clinical trial in patients with GAD has just started recruiting subjects (NCT03829241).

7. Phytochemicals

The pool of natural medicines that are traditionally used for reducing anxiety symptoms is wide-ranging and new natural plant compounds and plant extracts are being studied in order to identify novel treatment strategies (Fedotova et al., 2017; Savage, Firth, Stough, & Sarris, 2018). Anxiolytic effects are reported following administration of natural compounds and formulations derived from *Piper methysticum* (kava), *Centella asiatica* (pennywort), *Humulus lupulus* (hops), *Ginkgo biloba* (maiden hair), *Matricaria chamomilla* (chamomile), *Melissa officinalis* (lemon balm), *Passiflora incarnata* (maypop), *Scuterllaria leriflora* (skullcap), *Valeriana officinalis* (valerian), *Withania somnifera* (ashwagandha), *Magnolia officinalis* (magnolia bark) and *Lavendula angustifolia* (lavender), among others. While several classes of phytochemicals are already considered in cases of mild anxiety or as supplements to conventional anxiolytic therapies, the anxiolytic effects of phytochemicals have been demonstrated predominantly in studies involving animal models (Fedotova et al., 2017), and the structure-activity relationships, metabolism, absorption and neuropharmacological mechanisms are not clear in most cases. However, modulation of the GABA system has been revealed as one important mechanism of several phytochemicals (Savage et al., 2018). There is also the idea that multiple active ingredients may be synergistically effective, acting through independent but ideally complementary pathways to confer maximal effects while single compounds showing anxiolytic properties may represent promising lead substances for the development of novel anxiety-reducing drugs (Dias, Urban, & Roessner, 2012). Overall, the small number of clinical trials so far, and their limited sample sizes (see below), indicate that further examination of anxiety-reducing herbal preparations in terms of efficacy and safety is required in large-scale studies. Despite this limited evidence, a proportion of anxiety patients are known to favour alternative therapies, including phytotherapy (McIntyre, Saliba, Wiener, & Sarris, 2016). This preference can be of concern, as particularly patients with severe anxiety disorders may not be receiving the most suitable treatment. So far, in terms of the assessed clinical evidence of anxiolytic efficacy of phytochemicals, one plant stands out: kava.

7.1. Kava

Traditionally used in the South Pacific for religious and tribal ceremonies, kava (*Piper methysticum*) has gained interest in the western world for recreational and medicinal purposes. The main bioactive constituents of kava extract are six kavalactons (=kavapyrones) present in the rhizomes, roots and root stems of the kava plant. Of these, kavain and dihydrokavain have the strongest anxiolytic potential, thought to be mediated via the positive allosteric modulation of BDZ-sensitive and -insensitive forms of GABA-A receptors (Chua et al., 2016). Furthermore, kava has been shown to inhibit voltage-gated sodium and calcium channels and to increase extracellular levels of noradrenaline and dopamine and possibly acetylcholine transmission (White, 2018).

A Cochrane meta-analysis of the anxiolytic efficacy of kava, including seven placebo-controlled trials, revealed a small, though significant, overall effect size on the reduction in the anxiety rating in patients with neurotic, non-psychotic, generalised or pre-operative anxiety receiving kava extract (Pittler & Ernst, 2003). Subsequent trials in patients with GAD also reported a greater decrease in anxiety scores with kava than with a placebo that already exerted a strong effect (Connor, Payne, & Davidson, 2006). Different dosing regimens and extracts were used in the clinical trials, and this could have had an impact on the variable outcome of the studies. Kava does not elicit acute anxiolysis comparable to a BDZ, but reduces anxiety measures within a week of treatment (Gastpar & Klimm, 2003; Volz & Kieser, 1997). Nevertheless, a recent meta-analysis revealed that the current evidence is promising, but still insufficient to support claims of superior effectiveness of kava over placebo in GAD (Ooi, Henderson, & Pak, 2018). It is hoped that a recently completed Phase 4 trial will help to provide further evidence (NCT02219880). Data are not yet available. So far, a systematic review supports the use of kava for the short-term treatment (up to eight weeks) of anxiety, but points out that it is not a replacement for prolonged anti-anxiety drug use (Smith & Leiras, 2018). Although the ban by some European countries at the beginning of the 21st century on kava products for human consumption due to cases of hepatotoxicity has subsequently been lifted, e.g. in Germany, safety concerns around long-term consumption of kava remain.

7.2. Other plants in clinical development

So far, the influence on anxiety of three other plant extracts has been evaluated in randomised clinical trials. The efficacy and tolerability of **chamomile extract** *(Matricaria recutita)*, administered for 8–12 weeks, has been studied in outpatients with GAD in two randomised trials (Amsterdam et al., 2009; Mao et al., 2016) and one open-label study (Keefe, Mao, Soeller, Li, & Amsterdam, 2016). It was found that chamomile was safe and efficacious in reducing anxiety symptoms in moderate GAD cases, but did not affect the rate of relapse. Four weeks of treatment with **hops** *(Humulus lupulus)* caused a greater reduction in self-reported anxiety, depression and stress symptoms in healthy young adults in comparison with a placebo (Kyrou et al., 2017). Likewise, **saffron extract** *(Crocus sativus)* demonstrated a treatment effect on the Beck Anxiety Inventory questionnaire in subjects

with anxiety in comparison with a placebo at the 12-week time-point. Prompted by preliminary findings of positive effects of **echinacea** *(Echinacea angustifolia)* on anxiety in healthy participants (Haller et al., 2013), an ongoing randomised clinical trial (NCT03463018) is studying the effect of a root extract standardised in terms of its content of echinacosides and alkamides (Anxiocalm) on sub-threshold and mild anxiety individuals who are not eligible for anxiolytic medication (Table 2). Finally, the most recent clinical study involving a phytochemical compound for the treatment of an anxiety disorder was published in early 2019. The active constituent of the traditional Mexican medicine *Galphimia glauca* (popularly known as Corpionchi or Golden Bouquet) is the nor-seco-triterpene Galphimine-B that does not affect the GABA system, but acts on the dopaminergic neurons in the ventral tegmental area via NMDA receptors in rats (Jimenez-Ferrer, Herrera-Ruiz, Ramirez-Garcia, Herrera-Arellano, & Tortoriello, 2011). It was reported that the standardised extract containing 0.374 mg of Galphimine-B per dose demonstrated similar efficacy in reducing anxiety, but better tolerability after four and 10 weeks of treatment as compared with the active comparators lorazepam and alprazolam (Herrera-Arellano et al., 2007; Romero-Cerecero et al., 2019).

8. Pharmacological augmentation of psychotherapy

Although techniques such as mindfulness-based therapy show some positive effects in anxious patients (Hilton et al., 2017; Norton, Abbott, Norberg, & Hunt, 2015), and psychological treatments such as cognitive bias modification, targeting attention bias or interpretative bias, and a number of others have been introduced (Cristea, Mogoase, David, & Cuijpers, 2015), CBT, focusing on exposure to feared cues to promote extinction learning (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014), continues to be the most widely used and most strongly validated psychotherapeutic treatment for both youth and adult anxiety disorders (Barry, Yeung, & Lau, 2018; Kodal et al., 2018). CBT is an umbrella term for different techniques that cause a change in the patient's thinking about and behaviour towards feared stimuli, using behavioural methods to attenuate or eliminate the anxiogenic properties of external and interoceptive stimuli (Kaczkurkin & Foa, 2015). Thus through these therapies that incorporate an exposure element the individuals learn to approach internal and external feared stimuli rather than avoid them. There is ongoing development to implement novel variations of such psychological treatments to optimize therapeutic outcomes (Craske, Hermans, & Vervliet, 2018; Guastella, Norton, Alvares, & Song, 2018; Lebois et al., 2019; Weisman & Rodebaugh, 2018). The disadvantage of psychotherapeutic programmes is that apart from the fact that they are often insufficiently available, they are time-consuming and require extensive training of the therapist. Furthermore, CBT is not efficacious or acceptable for all patients, as demonstrated by considerable rates of partial or non-response (the mean rate is 35–54% in meta-analyses) as well as of non-adherence (Loerinc et al., 2015; Taylor et al., 2012). Hence, a common strategy to improve efficacy has been to combine psychotherapy with existing anxiety medication treatment. This approach, however, does not seem to provide consistently superior benefits across anxiety disorders, but may be useful for those patient groups that do not adequately respond to CBT alone (Etkin et al., 2019; Tolin, 2017). Recent rational, potentially more promising, examples of combination approaches of psycho-and pharmacotherapy are outlined below.

8.1. Facilitating fear-extinction mechanisms

The pharmacological boosting of fear extinction over fear memory retrieval (Singewald, Schmuckermair, Whittle, Holmes, & Ressler, 2015) in exposure-based forms of CBT is a promising approach that has been gaining momentum recently. Fear extinction involves learning that the feared aversive events do not occur when the conditioning stimulus is encountered. Formation of a new associative “non-fear” memory depends on protein synthesis, long-term potentiation and long-lasting synaptic plasticity and has been shown to be often deficient in patients with anxiety- and related disorders (He et al., 2018). Several molecular pathways have been revealed to be essential for extinction memory consolidation including the MAPK/Erk, PIK/Akt, and BDNF (Singewald et al., 2015; Tronson, Corcoran, Jovasevic, & Radulovic, 2012), while there is evidence that BDZ-associated mechanisms may disrupt the extinction learning process (Rothbaum et al., 2014). Targeting the underlying cause of this deficiency is suggested not simply to palliate fear and anxiety symptoms, but to tackle more closely the neurobiological root of the problem, i.e. alterations in the structure, function and connectivity in the anxiety/fear neurocircuitry along with neuroplastic and neurochemical alterations (see Section 4). In animal studies, activation of ionotropic NMDA receptors that stimulate the MAPK/Erk pathway via Ca^{2+} influx has been shown to be highly relevant in building extinction memory, indicating a promising candidate mechanism to target. Indeed, the partial NMDA receptor agonist **D-cycloserine** (DCS) is currently the most studied adjunct to EBT in off-label use. While DCS is not anxiolytic per se, it has been shown to facilitate fear extinction in rodents although fear recovery was still seen under certain conditions following cycloserine-promoted extinction (Richardson, Ledgerwood, & Cranney, 2004; Walker, Ressler, Lu, & Davis, 2002). After first promising results in patients with acrophobia (Ressler et al., 2004), DCS augmentation of EBT has been studied in patients suffering from SAD, specific phobias, PD, and PTSD, reporting variable effects. The most recent meta-analysis attributes only small, if at all, clinical effects of DCS augmentation of EBT for the treatment of anxiety disorders, OCD or PTSD (Burkner, Bittner, Holling, & Buhlmann, 2017; Mataix-Cols et al., 2017; Stojek, McSweeney, & Rauch, 2018). Even taking all of these findings into account, the full potential of DCS to facilitate extinction in human anxiety and PTSD patients is not entirely clear yet. One problem is that studies use different readouts of success (for instance, some use speed of treatment gains while others use response rate), and there is also the danger of strengthening fear memory reconsolidation if only insufficient fear reduction in within-session extinction learning is achieved (Hofmann, Otto, Pollack, & Smits, 2015; King et al., 2018). Furthermore, the benefit of DCS-augmented EBT seems to be reduced in patients receiving antidepressants (King et al., 2018; Otto et al., 2016). There is currently a Phase 1 trial aimed at studying the potential of DCS-augmented EBT to alleviate public speaking-induced anxiety (Table 2). Another NMDA receptor-activating small molecule, NYX-783, has been shown to enhance synaptic plasticity and to facilitate extinction learning in preclinical models, suggesting that it might be a candidate for clinical development as a treatment for PTSD. So far, NYX-783 has demonstrated high oral bioavailability and has been well tolerated across a wide dose range in a Phase 1 study involving healthy human subjects (https://www.aptinyx.com/pipeline/). The FDA has granted Aptinyx a fast-track designation for the development of NYX-783 in the treatment of PTSD (Anonymous, 2018).

Fear-extinction-facilitating effects have also been reported for **MDMA** in rodents (Young, Andero, Ressler, & Howell, 2015; Young et al., 2017) and in healthy humans (NCT03181763). The entactogen MDMA (3,4-methylenedioxymetamphetamine, ecstasy) increases central levels of 5-HT and, to smaller extents, of dopamine and noradrenaline by inducing transporter-mediated presynaptic release of these monoamines via activation of the trace amine-associated receptor 1 and the vesicular monoamine transporter 2 and by blockade of the corresponding transporters SERT, DAT and NET (Berry, Gainetdinov, Hoener, & Shahid, 2017; Carhart-Harris & Nutt, 2017). Upon this initial net effect, however, MDMA-induced 5-HT neurotoxicity may occur in response to high and/or repeated dosing (Vegting, Reneman, & Booij, 2016). The typical psychotropic and cardiostimulant effects have been attributed foremost to these monoamines, as well as to effects produced by their interaction with other transmitters/modulators such as OXT, vasopressin, cortisol and prolactin. In relation to fear and anxiety, MDMA has been mainly investigated as a psychotherapeutic adjunct

in the treatment of PTSD so far. It is, for example, suggested that MDMA may allow the patient to work on his/her trauma without experiencing overwhelming feelings of fear during the psychotherapeutic session. Meanwhile, six Phase 2 randomised clinical trials revealed clinically relevant reductions in PTSD symptoms, as well as safety of use, and the symptom reduction lasted for almost 3.5 years after treatment (Mithoefer et al., 2013; Mithoefer et al., 2018). When low/moderate doses of MDMA were given as a psychotherapeutic adjunct for the treatment of PTSD in a clinical setting, only mild adverse effects and a low abuse potential were reported (Feduccia, Holland, & Mithoefer, 2018). On the basis of these results, large-scale Phase 3 studies were approved by the FDA in November 2018 (Table 2; (Mithoefer et al., 2019)). In patients with refractory PTSD, a preliminary meta-analysis has recently revealed greater efficacy of MDMA-assisted psychotherapy compared to prolonged exposure therapy (Amoroso & Workman, 2016). This effect is proposed to be mediated via different mechanisms including the enhancing of arousal, promoting neuroplasticity and altering the neuronal activity of interconnected key brain areas of the extinction neurocircuitry (increased activity in the ventromedial PFC and decreased activity in the amygdala) likely via enhanced brain levels of monoamines and OXT (Feduccia and Mithoefer, 2018; Petschner et al., 2018). At the same time, MDMA may also interfere with the reconsolidation of the fear memories during psychotherapy (Hake et al., 2019). Furthermore, the anxiolytic effects of MDMA (see below) may increase tolerability of exposure therapy.

Similarly, **OXT**'s prosocial and trust-enhancing properties could make it also useful for combination with EBT. There are very few studies in clinical populations assessing the effect of OXT as a possible outcome enhancer in psychotherapy. In healthy participants, intranasal OXT has been shown to facilitate the extinction of conditioned fear (Acheson et al., 2013; Eckstein et al., 2015). This coincides with reduced amygdala activity in response to negative stimuli (Eckstein et al., 2015; Striepens et al., 2012) and with an increased functional connectivity between the amygdala and the dorsomedial PFC (Eckstein et al., 2015). Two small studies involving OXT augmentation for EBT in patients with SAD (Guastella, Howard, Dadds, Mitchell, & Carson, 2009) and arachnophobia (Acheson, Feifel, Kamenski, McKinney, & Risbrough, 2015) had disappointing preliminary outcomes. However, since intranasal OXT promotes both fear and extinction learning, the precise point at which it was administered may have been critical, as it has been learned with DCS augmentation of EBT (see above). Finally, stimulated by positive results of a pilot study (Yazker & Klein, 2010), two recent studies report beneficial effects of OXT in trauma-exposed subjects with high acute PTSD symptoms (Flanagan, Sippel, Wahlquist, Moran-Santa Maria, & Back, 2018; van Zuiden et al., 2017). These effects have been suggested to be due to OXT's interference with fear (reconsolidation) rather than being a result of promoting extinction mechanisms. Hence, any final evaluation of the potential of OXT as an adjunct to EBT is dependent on further investigations.

The **eCB system** that is introduced in detail in Section 6 also holds promise as an extinction-enhancing target. Mounting preclinical data demonstrate that activation of the eCB system using FAAH and MAG-L inhibitors or CB_1 receptor agonists enhances fear extinction while its pharmacological or genetic inactivation impairs fear extinction (Patel et al., 2017). In a direct translation of rodent findings, the FAAH inhibitor PF-04457845 was shown to improve the recall of fear extinction memories in healthy adults (Mayo et al., 2019). Also THC has been shown to facilitate fear extinction in healthy humans and in PTSD patients (Lisboa et al., 2019). Stimulated by a study in healthy participants showing that CBD enhances fear extinction, there is now the first randomised controlled clinical trial registered to investigate whether the addition of CBD to exposure therapy is effective in reducing phobic symptoms in treatment refractory patients with SAD or PD with agoraphobia. The study protocol is now available (van der Flier et al., 2019).

Finally, another promising novel strategy for augmenting EBT involves the **dopamine system**. Animal data showing that dopaminergic mechanisms and pathways arising in the ventral tegmental area are not only important (Abraham, Neve, & Lattal, 2014; Haaker et al., 2013; Whittle et al., 2016), but also necessary (Luo et al., 2018; Salinas-Hernandez et al., 2018) for successful fear extinction have raised the idea that increasing central dopamine availability might facilitate fear extinction. Indeed, boosting dopamine signalling with systemic administration of the dopamine bioprecursor L-3,4-dihydroxyphenylalanine (**L-DOPA**) accelerates fear extinction and reduces fear relapse in humans (Gerlicher, Tuscher, & Kalisch, 2018; Haaker et al., 2013), in particular in conditions when low fear is displayed at the end of the extinction session (Gerlicher, Tuscher, & Kalisch, 2019). So far, the proposed mechanisms of action of dopamine in fear extinction is that it encodes a prediction error (reward-like) signal (Abraham et al., 2014; Gerlicher et al., 2018; Salinas-Hernandez et al., 2018) and promotes extinction-related neuronal plasticity in the IL and amygdala (Haaker et al., 2013; Kalisch, Gerlicher, & Duvarci, 2019; Luo et al., 2018). Furthermore, in humans post-extinction L-DOPA increases the spontaneous reactivations of extinction-induced activity patterns in the ventromedial PFC after fear extinction learning and attenuates activation of the amygdala (Gerlicher et al., 2018; Haaker et al., 2013). Since a single dose of L-DOPA was able to also rescue deficient fear extinction in a clinically relevant mouse model of impaired fear extinction (Whittle et al., 2016), the question of whether these encouraging data can be transferred to clinics is currently being addressed in a randomised clinical trial studying the 'Dopamine Enhancement of Fear Extinction Learning in PTSD' (NCT02560389).

8.2. Targeting fear-memory-(re)consolidation mechanisms

Research elucidating the protein-synthesis-dependent processes underlying the formation and maintenance of fear and extinction memories has revealed that maladaptive associative fear memories can be destabilised and edited (for a recent review see Phelps & Hofmann, 2019) upon their retrieval, when memories enter a transient, labile state preceding reconsolidation processes. These processes can be weakened by pharmacological interference – for example, by modulating noradrenergic transmission. The β-adrenoceptor blocker **propranolol** has long been used to reduce the autonomic symptoms accompanying anxiety while the efficacy of the α_1-adrenoceptor blocker **doxazosin** in reducing PTSD symptoms is currently being investigated (Table 2). Propranolol is the most widely studied compound in regard to both the potential blocking of memory consolidation following trauma (Amos, Stein, & Ipser, 2014) and the interference with reconsolidation mechanisms. However, these studies have yielded mixed results (Walsh, Das, Saladin, & Kamboj, 2018). Beneficial effects of combining propranolol with trauma reactivation have been reported in a recent small randomised controlled trial (Brunet et al., 2018) as well as in three earlier pilot studies (Brunet et al., 2008; Pitman et al., 2002; Vaiva et al., 2003); however, negative outcomes have also been reported (Hoge et al., 2012; Wood et al., 2015). In the short-term treatment of patients with PD with and without agoraphobia, propranolol was shown to elicit similar anxiety symptom reduction as BDZs (Steenen et al., 2016); a Phase 2 trial is currently elucidating its potential as an adjunctive to CBT, which would represent a new intervention for PD (Table 2). The glucocorticoid receptor antagonist **mifepristone** and the mTOR inhibitor **rapamycin** have also been proposed to interfere with reconsolidation mechanisms, which is, however, not supported in clinical studies, e.g. in patients with PTSD (Walsh et al., 2018). An ongoing clinical trial evaluates whether the potential effects of mifepristone on memory reconsolidation can be augmented with DCS (NCT02099825). Overall, pharmacological strategies for interfering with fear reconsolidation appear to be viable, but data are insufficient and variable, and thus do not support their clinical application at present.

8.3. Improving adherence to psychotherapy

One of the problems of psychotherapy is the non-adherence of the patients that is driven by various factors including low motivation for treatment, poor readiness for change and poor therapeutic alliance (Taylor et al., 2012). Here, the use of specific drugs with mind-changing properties is hoped to provide improvement. For example, the classic serotonergic psychedelics **LSD** and **psilocybin** (magic mushrooms) have been shown to alter the state of consciousness in a way that is thought to be helpful during psychotherapeutic interventions (Liechti, 2017). Drug effects include positive mood appraisal, altered consciousness, openness towards others and arousal. Both drugs are agonists at 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors with varying affinities, whereby the full or partial agonism at the 5-HT_{2A} receptor is likely to be the necessary site of action for eliciting an altered state consciousness including prosocial and pro-cognitive effects. Importantly, 5-HT_{2A} receptor signalling has also been implicated in processes of neuroplasticity, such as neurogenesis, neurodevelopment, learning, including extinction learning, cognitive flexibility and enhanced environmental sensitivity (Liechti, 2017). From the 1950s to the 1970s there was some reported indication of beneficial effects of psychedelic drugs on anxiety in cancer patients. However, due to regulatory restraints and stigma associated with these agents it was not until recently that their potential benefit for anxiety treatment in different disorders was investigated in a few small clinical trials (Dos Santos, Bouso, Alcazar-Corcoles, & Hallak, 2018). A significant and sustained decrease of anxiety scores in patients with life-threatening diseases has been reported in an open-label randomised study following LSD-assisted psychotherapy (Gasser, Kirchner, & Passie, 2015). This finding needs replication in larger trials, and these are currently ongoing (NCT03153579, Table 2). Likewise, modest to high doses of psilocybin have been shown to rapidly reduce clinical signs of anxiety and depression in cancer patients (Griffiths et al., 2016; Ross et al., 2016) and in patients with treatment-resistant depression (Carhart-Harris et al., 2016) receiving psychotherapeutic support for up to six months. Finally, there is also some initial evidence that psilocybin may be beneficial in OCD (Moreno, Wiegand, Taitano, & Delgado, 2006), and this is now being further explored in two Phase 2 trials using lorazepam and niacin as comparators (NCT03356483, NCT03300947, Table 2). The results of these studies are interpreted in the direction that the use of a single dose of either LSD or psilocybin in a controlled clinical setting can considerably improve the quality of life of patients in parallel with relatively few side effects and a low prevalence of abuse, arguing for the reclassification of psychedelics (Johnson, Griffiths, Hendricks, & Henningfield, 2018; Johnson, Hendricks, Barrett, & Griffiths, 2019).

MDMA, apart from its fear-extinction-facilitating effects (see above), exerts entactogenic effects, i.e. it enhances feelings of love, happiness and closeness to others (Simmler & Liechti, 2018) and has been shown to elicit rapid anxiolysis in animals and in humans (Feduccia et al., 2018). For example, it has been reported that negative emotional pictures were perceived as less aversive after a single dose of MDMA in healthy humans (Kuypers, Dolder, Ramaekers, & Liechti, 2017). Due to its anxiolytic, self-esteem-raising and prosocial properties, MDMA may also be of interest for the treatment of anxiety in other disorders. For instance, MDMA has demonstrated anxiolytic effects when administered to patients suffering from a life-threatening illness (Liechti, 2017), and it has been found to reduce social anxiety in adults with autism spectrum disorder (Danforth et al., 2018; Danforth, Struble, Yazar-Klosinski, & Grob, 2016).

It should be noted that the mechanism(s) of the acute anxiolytic effects of LSD, psilocybin and MDMA are not clear, but are thought to involve common changes in the functional connectivity of key substrates of the anxiety/fear neurocircuitries (Carhart-Harris & Nutt, 2017) and attenuated reactivity of the amygdala (Grimm, Kraehenmann, Preller, Seifritz, & Vollenweider, 2018; Kraehenmann et al., 2015; Mueller et al., 2017).

9. Summary and conclusion

This review has summarised novel pharmacological strategies to treat anxiety and anxiety-related disorders either as a substitute for, or to complement, existing traditional treatments, which have clear limitations in terms of efficiency and their side-effect profile. We presented the most promising drug development candidates, focusing on those that are currently being investigated in clinical trials for different anxiety-related disorders (Table 2) and that exert, either alone or in combination, acute, delayed and/or sustained relief of anxiety symptoms (Fig. 4). Approximately 20 pharmaceutical companies as well as several academic consortia (Table 2) are involved in these trials at present, reflecting the rekindled interest and renewed optimism after a period of disengagement by some of the major traditional pharmaceutical firms from this field in the past. After pregabalin and duloxetine were last approved for the treatment of GAD in 2006 and 2007, respectively, no other drug was successful in completing clinical development for the treatment of anxiety and related disorders. Currently, 12 compounds have entered Phase 3 of clinical development, 25 compounds are in Phase 2 and eight compounds are in Phase 1 for the treatment of different forms of anxiety and trauma-related disorders, as summarised in Table 3. Interestingly, most drugs are evaluated for the indication PTSD, and this may reflect a particularly urgent need for novel pharmacotherapies to reduce disease-associated symptoms and improve the quality of life in this particular patient cohort.

One current strategy for the improvement of existing anxiolytic drugs, mainly serotonergic and prototypical GABAergic BDZ compounds, is to increase target selectivity and, if necessary, to combine relevant targets leading to more selective multi-drug target approaches. Vilazodone is one such example of the refinement of serotonergic drugs for the treatment of GAD, resulting in an improved side-effect profile and apparently greater advantages in therapeutic onset as compared with SSRIs. The rapid-acting synthetic neurosteroid aloradine is an example of a refined agent targeting GABAergic mechanisms via the GABA-A receptor and represents a novel drug for on-demand treatment of SAD. Further progress in this field is also seen in the improvement of formulations that allow the application of optimised doses of refined or established anxiolytic drugs that then preferentially target receptors of interest rather than off-target receptors that get recruited at higher doses. Examples are new formulations of cyclobenzaprine and gepirone.

A more innovative approach involves the search for compounds with novel mechanisms of anxiolytic action using the growing knowledge concerning the relevant fear and anxiety-related neurocircuitries and neurobiological mechanisms (Section 4). JNJ-42165279, SRX-246, ketamine and DCS are examples that have evolved from this increased understanding. In general, evaluated targets include the glutamate, eCB and neuropeptide systems, ion channels, as well as phytochemicals, though the glutamate system as a target may hold particular promise for mediating rapid and large anxiolytic effects, even in patients who are resistant to established therapy. Such promising novel candidates include ketamine, riluzole and xenon, all modulating glutamatergic neurotransmission. While ketamine and xenon inhibit NMDA receptors, riluzole and its prodrug troriluzole increase the clearance of glutamate and decrease glutamate release. In particular, the studies involving ketamine suggest that greater efficacy and more rapid onset than with current first line pharmacotherapy (e.g. SSRIs) are possible in different anxiety disorders, and even in treatment-resistant patient populations. Regarding the cannabinoid system, randomised clinical trials, although limited in number, have revealed promising evidence of rapidly reducing anxiety symptoms through CB_1 receptor activation by natural or synthetic cannabinoids or the use of FAAH inhibitors including JNJ-42165279. The noted trend towards the off-label prescription of medicinal cannabis/marijuana or nabilone for patients with anxiety disorders may reflect the fact that there has been a considerable lag in developing really new and effective evidence-based treatments in this field, and in psychiatry in general (Kolar, 2018).

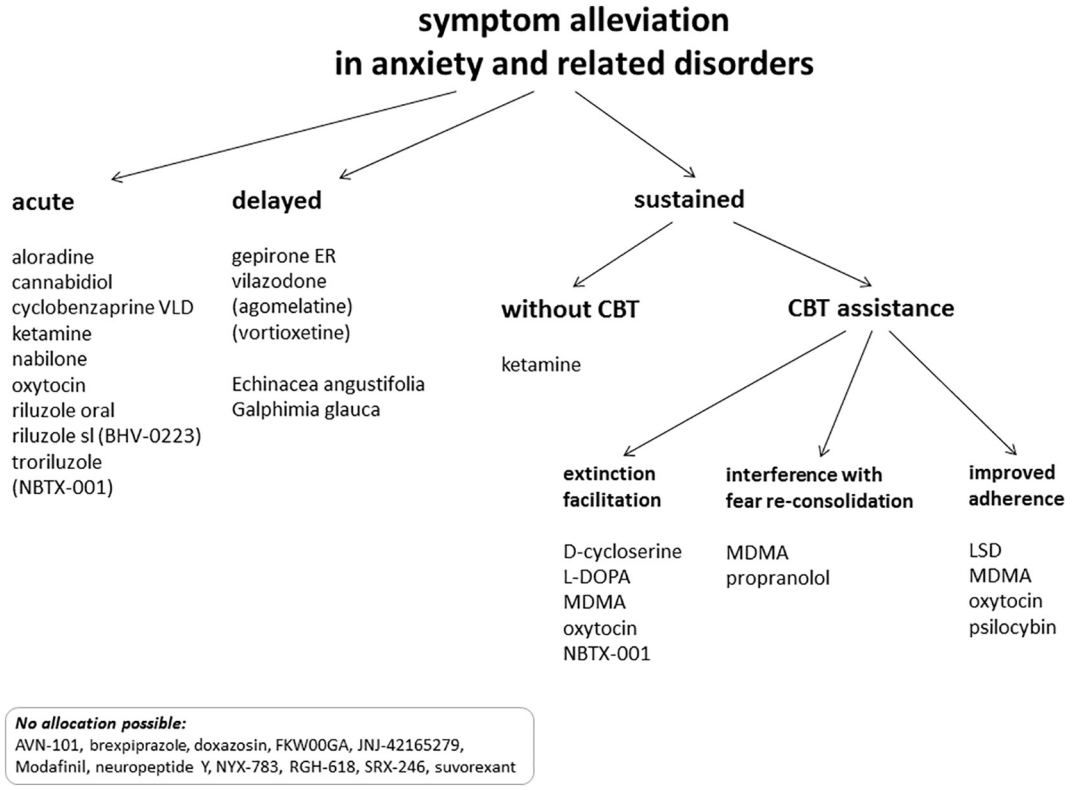

Fig. 4. Modes of therapeutic symptom alleviation in anxiety and related disorders by the drugs discussed in this review. Drug-induced relief in anxiety-related symptoms can be immediate (acute) or delayed requiring repeated treatment. Based on available data concerning novel drugs, examples of possible sustained symptom relief include mainly the combination of drugs with cognitive behavioural therapy (CBT) so far.

In parallel, approaches are being developed to more rationally utilise potential synergisms combining complementary behavioural/psychotherapeutic and pharmacotherapeutic approaches. In particular, putative learning and memory-enhancing drugs ('neuroenhancers') with or without anxiolytic properties have been shown to facilitate fear extinction - a central mechanism of EBT - by strengthening the formation of new inhibitory "no-fear" memories that compete with the original fear memories and their behavioural expression. Among those drugs, DCS is the most studied and is an example of successful research from bench to bedside, with promising outcomes in some clinical studies and specific anxiety disorders, but also negative results in others. Conclusions derived from these studies have retrospectively helped to refine DCS-assisted EBT and are guiding the development of other candidates to facilitate fear-inhibitory learning, such as MDMA and L-DOPA. Moreover, additional acute anxiolytic properties of such extinction-enhancers may be advantageous for increasing patients' tolerability of and, thus, adherence to EBT. Along these lines, but based mainly on a low number of pilot clinical trials, there has recently been a kind of revival of the potential medicinal use of psychedelics, including LSD and psilocybin, as potential adjuncts to psychotherapy in anxiety treatment. Many of these new treatments have not been yet sufficiently clinically investigated in terms of their long-term safety, and there are concerns about the risk of dependence with the above-mentioned psychedelics, but also with the use of ketamine, MDMA, medicinal cannabis/marijuana and synthetic cannabinoids. This risk needs to be investigated in detail – for example, by administering these drugs to pre-screened patients (with no history of drug abuse) in a clinical, controlled framework at the recommended low-moderate doses. Nevertheless, there are a number of scientific, political and ethical questions that remain and, thus, the use of these agents, particularly the psychedelics, will be likely advanced with caution.

There are also considerations concerning adjustment of general drug development strategies in this field. Over the last few decades, anxiolytic drug discovery focused on the utilisation of single targets. However, the expectation that highly selective agents acting on specific molecular targets would yield better and safer psychiatric drugs has not been realised (Griebel & Holmes, 2013; Millan, Goodwin, Meyer-Lindenberg, & Ove Ogren, 2015). Interestingly, some of the drug candidates in development, such as aloradine, xenon-gas, MDMA, agomelatine, psychedelics and kava constituents, represent multimodal drugs. The shift in drug discovery to multi-target approaches is also increasingly being promoted in other CNS research areas, such as neurodegenerative disorders (Anighoro, Bajorath, & Rastelli, 2014; Ramsay, Popovic-Nikolic, Nikolic, Uliassi, & Bolognesi, 2018; Zheng, Fridkin, & Youdim, 2014). In anxiety drug development, the multi-target approach, with the idea of more efficiently re-equilibrating perturbed circuits, is supported by the fact that anxiety disorders are polygenetic and associated with disturbances in multiple complex neuronal systems (Bandelow et al., 2016; Millan, 2003). Furthermore, the presence of other psychiatric and somatic diseases also need consideration in the medical treatment of anxiety patients. This may be achieved by combining several target specific drugs, termed polypharmacy, that is widely used in the clinical/outpatient setting with the risk of more and/or more severe side effects due to drug-drug interactions. Alternatively, multi-target drugs address several biological targets and may either treat two aspects of the disease (e.g. propranolol reduces somatic symptoms and interferes with fear re-consolidation in PTSD patients, see Section 8) or produce additive and even synergistic effects. Ideas following this latter polypharmacological approach involve rational combinations of, for example, transferring a non-monoaminergic drug target mediating rapid anxiolysis (such as NMDA receptor antagonism by ketamine) into a refined molecule with a serotonergic profile (e.g. vilazodone) and may potentially lead to improved anxiolytic treatments (Olivier, 2015).

Taken together, after years of stagnation in drug discovery in this field (Griebel & Holmes, 2013), the examples of progress outlined in

this review encourage renewed interest in anxiety drug development and increased optimism that more effective treatments for anxiety and related disorders, the most prevalent mental disorders, are on the horizon.

10. Future direction

While some promising drug candidates for anxiety treatment are in clinical development, further success in selecting the next generation of anxiolytic drugs and importantly improving treatment outcomes (approaching full remission) as well as tolerability/safety will rely on a number of factors. The finding that current first line treatments proved ineffective for a considerable proportion of patients indicates the need to change treatment strategies, for example with a shift to the development of targeted individualized treatments. Furthermore, it will be important to enable better translation between preclinical and clinical research using new conceptional approaches to diagnose anxiety-related disorders, as well as back-translation to aid future improved (animal) model development. This, and the ability to link pathological anxiety more closely to underlying neurobiology will only be possible by countering the problems arising from the complexity of anxiety disorders with the help of improving the selection of appropriate target population to be treated (see below) and by enhancing dedicated, multi-disciplinary efforts that bring together expertise in chemistry, physiology, pharmacology, psychiatry, (*epi*)genetics, machine learning, ethics and other fields. Examples of areas that should receive specific attention in future anxiety drug discovery and development are outlined below:

10.1. Biomarkers and personalized treatment

Problems associated with the heterogeneity within a given anxiety disorder as classified presently, together with inaccurate subgroup stratification tools have likely hampered the development of novel anxiolytic drugs with improved treatment outcome. Future drug development and treatment optimization will critically rely on the further identification and use of objective biomarkers in clinical settings to better classify patient subpopulations (biosignature development) and stratify to specific treatments aiding clinical trial design, as well as to predict therapy outcomes including treatment resistance. These approaches as a route to better diagnosis, respective improved personalized treatment and anticipated increased success probability in clinical trials (Wong, Siah, & Lo, 2019) are increasingly studied (Deckert & Erhardt, 2019; Maron et al., 2018; McNaughton, 2018; Woo, Chang, Lindquist, & Wager, 2017). At present, however, none of the putative blood-based, genetic, epigenetic, neurochemical, metabolic or neuroimagery biomarkers are sufficiently specific, valid and reliable as diagnostic tools or markers of treatment response in anxiety disorders (Bandelow et al., 2016; Lueken et al., 2016; Maron et al., 2018), affording, for the moment, a rational combination (panel) of proposed biomarkers and ongoing future efforts in this field. These efforts, as well as better biological demonstration of target engagement by treatments will lay the foundations for biologically based precision medicine (Bzdok & Meyer-Lindenberg, 2018). Although such precision medicine is clearly in its infancy, its progress will likely also be facilitated by the consideration of alternative diagnostic systems such as the RDoc system by focusing on the negative valence domain as construct for anxiety [see Section 3; (Nicholson & Sommer, 2018)]. These efforts, over time, will help in the development of drugs targeting the underlying dysfunctions of individual patients more precisely and will help to improve the understanding of treatment-response heterogeneity involving pharmacogenomics (Lauschke, Zhou, & Ingelman-Sundberg, 2019) and thus the identification of treatment responsive subgroups of patients. For example, polymorphisms in the 5-HT transporter, as well as in the 5-HT_{1A}, 5-HT_{2A} and 5-HT_3 receptors, have been reported in different anxiety disorders, likely influencing the efficacy of 5-HT-based pharmacotherapy (Helton & Lohoff, 2015). Along these lines it will be important to further improve information on drug response variation and drug-drug interaction involving, for example gene polymorphisms in the cytochrome P450 system (Aldrich et al., 2019). Thus, this kind of personalized medicine has great potential to improve pharmacotherapy for patients suffering from different forms of anxiety disorders in the future.

10.2. Circuit level approaches

As mentioned, anxiety patients display changes in processing of information in relevant neuronal pathways and networks which will be further characterized using novel methods (see e.g. (Yang et al., 2019) and show sensitivity to existing anxiolytic treatments. Future therapies for anxiety disorders should aim at improved, more specific circuit-level approaches, to target activity with the aim of normalising identified aberrant function in relevant brain circuitries, which seems to be a key mechanism in successful inhibition of anxiety (see Section 4). The understanding of the role of the diverse and heterogeneous neurotransmitter/—modulator systems at the crucial nodes in the anxiety/fear neurocircuitries is important for identifying new targets for anxiolytic drugs, even when the drugs are systemically administered. The precise targeting of these specific neuronal populations with receptor subtype-selective ligands after systemic administration, in combination with novel drug-delivery techniques such as DART [drugs acutely restricted by tethering; (Shields et al., 2017)], will be a promising path to improvement in anxiety drug development. Whether (apart from evolving brain modulation techniques such as deep brain stimulation, transcranial magnetic stimulation, transcranial brain stimulation, and electroconvulsive therapy) future pharmacological anxiety treatment can and will make use of viral-mediated gene transfer of DREADDs to enable very precise targeting of brain activity and pathways is an open question and will depend on safety issues, among other factors.

10.3. Drug discovery process refinements

Following improvements in successful hit identification and validation, future anxiolytic drug discovery is also facing well known problems of CNS lead optimization including in particular overcoming of the blood-brain barrier which profoundly limits the oral administration of antibodies, peptides and polar molecules (Danon, Reekie, & Kassiou, 2019). Tools based on computational multi-parameter optimization algorithms (Wager, Hou, Verhoest, & Villalobos, 2016) can better predict favourable CNS drug properties in the future. Temporary blood-brain barrier disruption by ultrasonic techniques (Leinenga, Langton, Nisbet, & Gotz, 2016), intranasal administration (e.g. of peptides such as oxytocin) and more recently nanoparticles (Saeedi, Eslamifar, Khezri, & Dizaj, 2019) are potential alternative routes of CNS administration of non-blood-brain barrier penetrant agents in the future.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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