Anxiety levels and related pharmacological drug treatment: a memorandum for the third millennium

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Summary. Anxiety disorders frequently affect the general population and have a lifetime prevalence ranging from 13.6% to 28.8%. This paper reviews full articles dealing with the pharmacological treatments of generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder (PD) and post-traumatic stress disorder (PTSD). This review also attempts to evaluate the use of new drugs acting on several neurotransmitters involved in the pathophysiology of anxiety disorders. Major advances include the development of glutamatergic drugs for treating GAD and OCD. Further randomized controlled trials to test the effect of glutamatergic agents in the treatment of OCD and GAD would be warranted.

Key words: anxiety disorders, drug treatment, glutamatergic system.

Riassunto *(Sindromi ansiose e trattamento farmacologico: un promemoria per il terzo millennio)*. I disturbi d'ansia nella popolazione generale hanno una prevalenza che varia tra il 13,6% ed il 28,8%. Scopo del presente articolo è quello di esaminare l'attuale trattamento farmacologico dei disturbi d'ansia ponendo particolare attenzione al disturbo d'ansia generalizzato (GAD), al disturbo ossessivo-compulsivo (DOC), al disturbo di panico, ed al disturbo da stress post-traumatico (PTSD). Particolare attenzione è stata posta alle molecole che agiscono sui differenti sistemi neurotrasmettitoriali coinvolti nei meccanismi fisiopatologici dei disturbi d'ansia. Dati recenti sembrerebbero suggerire che i farmaci che agiscono sul sistema glutammatergico possano rappresentare una nuova prospettiva terapeutica nel trattamento del GAD e del DOC. I risultati preliminari, anche se incoraggianti, necessitano tuttavia di successive validazioni mediante studi controllati randomizzati.

Parole chiave: disturbi d'ansia, trattamento farmacologico, sistemi glutammatergici.

INTRODUCTION

Anxiety, a basic human emotion, is a physiological state characterized by cognitive, somatic, emotional, and behavioural components and an uncomfortable feeling associated with uneasiness, apprehension, or worry. Fear differs from anxiety, which is considered a generalized mood state occurring without an identifiable external triggering stimulus; fear is related to a specific behaviour of escape and avoidance and occurs in the presence of an external threat. If anxiety is excessive and interferes with everyday activities, it is considered a pathological condition and is classified as an anxiety disorder.

In the general population, anxiety disorders are frequent, with a lifetime prevalence rate ranging from 13.6% to 28.8% [1, 2]. Because of a high comorbidity rate with other psychiatric disorders and other medical conditions, the quality of life of these patients deteriorates, and the social disadvantage becomes comparable to that of chronic somatic disorders [3, 4].

The Diagnostic and Statistical Manual Fourth Edition-Revised (DSM-IV-TR) [5] classifies anxiety disorders as panic disorder (PD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and generalized anxiety disorder (GAD). Because the DSM-IV groups psychiatric disorders when they have common symptoms [6, 7], the intergroup variability increases. The current diagnostic criteria do not provide an optimal classification [8], and many proposals have been put forward to better classify mental disorders. The dimensional approach differs from the nosological approach, which classifies diseases according to specific symptoms; the dimensional approach relies on the fact that many disorders may have common symptoms [9] but that different psychopathological dimensions may underlie different syndromic categories. For each dimension, there will be a corresponding pathophysiological mechanism that can be more easily recognized in comparison to the category model. For example, instead of grouping together GAD and PD under the

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heading of "anxiety disorders" (as in the DSM-IV), GAD will be classified together with the major depressive disorder/dysthymia (in what Watson, 2005, labels the "distress disorders") because they share more similar with depressive disorders than with other anxiety disorders [10].

Regarding OCD, the situation is further complicated because OCD shares important features with a range of related syndromes that are considered to fall outside the current categories of mood and anxiety disorders. These overlapping features include similar symptoms, common etiological factors, and responsiveness to the same types of pharmacologic treatments. Such related syndromes have been labelled the "obsessive-compulsive spectrum disorders" [11]. Although distorted perceptions of fear are differently present among the anxiety disorders, this factor is not sufficient to justify their nosological integration. As an example, OCD does not appear to fit well with the other anxiety disorders because of its unique neurophysiopathology and because of the unfavourable outcome of psychological interventions.

PD with or without agoraphobia is a disabling condition with a negative impact on social, family, and working activities. It is characterized by recurrent unexpected attacks of severe anxiety accompanied by a number of somatic symptoms including palpitations, dyspnea, nausea, and vertigo. It is common in the general population, with a one-year prevalence of 2.7% and a lifetime prevalence of 4.7% [12]. The pathogenesis of PD is complex and comprises biologic, psychological, genetic, and environmental factors. A large number of studies have suggested that the serotoninergic and noradrenergic systems play an important role in the pathophysiology of PD [13]. Evidence from animal model studies of anxiety has led to the hypothesis that serotonin enhances inhibitory avoidance (related to anxiety) in the forebrain but inhibits one-way escape (panic) in the midbrain periaqueductal gray.

Increasing evidence indicates that the γ-aminobutyric acid (GABA) system is important in the pathophysiology of PD [14, 15]. Several studies have demonstrated that patients with PD have a dysfunction of the GABA-A receptors [16] or altered brain GABA concentrations (or both) [17]. There is also evidence that GABA-A receptor modulatory neuroactive steroids are altered in patients with PD [18].

GAD is a common and typically chronic mental disorder with a prevalence in the general population of around 6% [19]. It is characterized by inappropriate or excessive anxiety and worrying that persist over time and are not restricted to a particular set of circumstances. The pathophysiology is based on altered neurotransmission of serotonin, norepinephrine, GABA, cholecystokinin, and corticotropin-releasing factor. Recent studies have emphasized the hyperactivation of the amygdala, the involvement of the ventrolateral prefrontal cortex, and a glutamatergic dysfunction in the pathogenesis of GAD [20]. However, it is also associated with reactivity to and avoidance of internal experience [21].

OCD is a chronic and often disabling disorder with a prevalence rate of 2-3% of the worldwide population [22]. It is characterized by repeated, uncontrolled obsessive thoughts and ritualistic behaviour and compulsions. A large body of evidence now suggests a serotoninergic basis of OCD. Moreover, functional imaging studies have also demonstrated a dysfunction of the cortico-striato-pallido-thalamo-cortical tract in OCD patients [23, 24] and in the anterior cingulate cortex. These regions receive a large amount of serotoninergic innervation from the raphe nuclei. The observation that at least 30% of OCD patients do not respond to specific serotonin reuptake inhibitors (SSRIs) indicates that more complex mechanisms might underlie the overall clinical heterogeneity of OCD patients [25, 26]. However, functional, structural, and spectroscopic brain imaging studies have suggested a dysfunction in both the "direct" and the "indirect" loops of the cortico-striato-pallido-thalamo-cortical circuits [27], where the predominant excitatory neurotransmitter is glutamate. Several studies [28, 29] have identified a glutamatergic dysfunction in this circuitry that may play a role in the development of OCD. Unlike the other anxiety disorders, OCD is now considered a neurodevelopmental disorder [30].

PTSD is a prolonged reaction to an extremely traumatic experience [31]. The lifetime prevalence in the United States is estimated to be 1.3-7.8% [32]. Two subtypes of trauma response have been hypothesized, one characterized predominantly by hyperarousal and the other primarily dissociative, each one representing unique pathways to chronic stress-related psychopathology [33]. Regarding hyperarousal responses, many studies have demonstrated the involvement of the anterior cingulate cortex [34, 35], the medial prefrontal cortex [36, 37], and the thalamus [38, 39], while the parietal [40], occipital, and temporal cortices [41] are implicated in dissociative processes.

EVIDENCE-BASED TREATMENTS FOR ANXIETY DISORDERS

Panic disorder

In the past three decades, a range of pharmacological treatments has been developed for PD. Imipramine was the first drug [42] used in the treatment of PD and along with clomipramine has been the most studied of the tricyclic antidepressant (TCAs) compound in the pharmacotherapy of PD [43, 44]. Because of their serious side-effects, irreversible monoamine oxidase inhibitors (MAOIs) such as phenelzine or tranylcypromine are generally reserved for patients who do not respond to other treatments [45] and are considered second-line choices [46]. Data regarding the efficacy of the reversible MAOI moclobemide are inconsistent, and it should be used as a third-line drug [47]. SSRIs are

currently considered the first drug of choice for the treatment of PD [48, 49]. Many studies have demonstrated the efficacy of citalopram [50], escitalopram [51], fluoxetine [52, 53], fluvoxamine [54], paroxetine [55], and sertraline [56-58]. There is no evidence of a differential efficacy within the SSRI class [59], whereas differences exist in side-effect profiles, drug interaction, and half-life [60]. Escitalopram has been shown in clinical trials to improve anxiety symptoms associated with depression, PD, and social anxiety disorder [61].

If a patient with PD does not respond to treatment with an SSRI, a trial with another SSRI should be attempted; if that fails, switching to venlafaxine, a TCA, or a benzodiazepine (BDZ) is recommended [62]. Many studies [63-65] have demonstrated the efficacy of high-potency BDZs (alprazolam and clonazepam) in the short-term treatment of this disorder while low potency BDZ (diazepam) may have an anti-panic effect at higher doses than normally prescribed for other anxiety disorders [66]. In a recent meta-analysis [67], the efficacy of TCAs, SSRIs, and BDZs was compared: 53 studies were analyzed for a total of 7725 patients. TCAs, SSRIs, and BDZs showed a similar effect in improving anxiety (symptoms and frequency of panic attacks) and agoraphobia, whereas SSRIs and TCAs were superior to BDZs in alleviating depression, as expected. Several meta-analytic reviews of the panic treatment outcome demonstrated that treatment effect sizes for Cognitive Behavioural Therapy (CBT) are equal to or surpass those for antidepressant or BDZ treatments [68]. CBT should be considered as an effective first-line treatment for the disorder and for patients who have partial improvement with pharmacotherapy [69].

General anxiety disorder

The efficacy of TCAs for the treatment of GAD has been demonstrated [70, 71], but their use is limited by their overall poorer tolerability in comparison with SSRIs and serotonin- (norepinephrine) reuptake inhibitors (SNRIs). Paroxetine [72, 73], citalopram [74], and escitalopram [75, 76] are the SSRIs approved by the US Food and Drug Administration (FDA). There are also trials demonstrating the efficacy and tolerability of sertraline [77, 78] in GAD, although it has not been approved by the FDA for this indication. Few studies [79] support the use of mirtazapine in GAD, as well as in GAD with concomitant major depressive disorder [80]. The SNRIs, however, are emerging as first-line medications [81]; short- and long-term controlled trials of venlafaxine [82, 83] and duloxetine [84, 85] have demonstrated the efficacy of these compounds in the treatment of GAD.

BDZs are generally used in the acute treatment of GAD [86], preferentially in those patients affected by somatic symptoms [87]. Another compound approved by the FDA for treating anxiety disorders is the partial 5HT1a agonist buspirone, which shows efficacy [88] and safety [89] in the treatment of GAD [90], including in a study comparing the efficacy of buspirone and tandospirone [91]. Regarding antiepileptic drugs, many trials [92, 93, 94] have proved the efficacy of tiagabine [95, 96] and of pregabalin [97], a structural analogue of GABA that has been recently licensed [98] for the treatment of GAD. The H1 antihistaminic drug hydroxyzine is effective in studies conducted for as long as 12 weeks in patients with GAD [99].

A few studies have investigated the use of antipsychotic monotheraphy in GAD: an open-label trial suggested the benefits of ziprasidone [100]; one controlled trial has shown the efficacy of flupenthixol in patients with refractory GAD [101]; and a few studies have investigated the tolerability of sulpiride [102, 103]. Recent controlled studies have demonstrated the efficacy of augmentation therapy with the atypical antipsychotics olanzapine and risperidone in patients with GAD who did not respond to another medication (SSRI, SNRI, BDZ, or other anxiolytic or antidepressant) [104, 105].

Obsessive compulsive disorder

SSRIs and CBT are first-line agents in the treatment of OCD. The first uncontrolled case series showing successful treatment with clomipramine appeared in the 1960s. Since 1991, multiple controlled studies [106, 107] have demonstrated clomipramine's efficacy in the treatment of OCD [108, 109]. Clomipramine is now recommended as a second-line treatment; in spite of an efficacy greater than that of SSRIs, clomipramine has more side effects. The efficacy and the tolerability of the SSRIs-fluvoxamine [110], sertraline [111], fluoxetine [112], paroxetine [113], and citalopram, has been proved by several placebo-controlled studies [114, 115], although long-term (i.e., more than 2-year) follow-up studies of OCD patients treated with SSRIs are rare.

CBT is a reasonable first-line therapy in less-severe forms of OCD [116], and it should be indicated in OCD patients with associated personality disorders or dissociative symptoms in addition to a pharmacological treatment [117]. For good efficacy in the treatment of OCD, a trial of SSRIs for a long duration (10-12 weeks) and at a high dose (often the maximum recommended dose) is often required. However 40% to 60% of patients with OCD disorder do not respond to adequate treatment trials with SSRIs. A strategy that has been used to enhance serotoninergic action is the use of alternative routes [118] of administration of SSRIs, such as intravenous administration [119]. Intravenous treatment with clomipramine [120] has been reported to be effective for OCD patients who do not respond to oral treatment with the same drug [121].

Other treatment options include switching, augmentation, and novel agent strategies. Multiple studies have demonstrated the efficacy of switching to another SSRI, to clomipramine, or to an SNRI such as venlafaxine. A double-blind controlled study compared the efficacy of the irreversible IMAO

phenelzine *vs*. fluoxetine in the treatment of refractory OCD patients [122]. One further treatment option is augmentation of an SSRI with another agent that works on other neurotransmitter systems or different serotonin receptors. According to National Institute For Health And Clinical Excellence (NICE) guidelines [123], the combination of a dopamine antagonist (typical or atypical) and an SSRI should be effective in treating refractory OCD. The side-effect profile of the atypical antipsychotic agents is less troublesome than that of the traditional neuroleptics. Multiple studies have demonstrated the efficacy of augmentation [124] with pimozide, haloperidol [125], risperidone [126-128], olanzapine [129, 130], and quetiapine [131, 132]. A few studies have evaluated the safety and efficacy of valproate [133, 134], gabapentin [135], and lamotrigine [136] in augmentation with an SSRI or a dopamine antagonist.

Post traumatic stress disorder

Given the high degree of comorbidity between PTSD and depression, and the common clinical features of PTSD and other anxiety disorders (anxiety, agoraphobia, panic attacks), it is not surprising that the majority of early research studies have focused on the efficacy of antidepressants for PTSD [137]. Three controlled trials and several uncontrolled studies examined the efficacy of the TCAs for PTSD symptoms, including studies of imipramine, desipramine, and amitriptyline. Four controlled trials and at least six uncontrolled reports demonstrate the efficacy of MAOIs for the treatment of PTSD, including trials with phenelzine, brofaromine, and moclobemide. Eight completed, controlled SSRI trials have been reported, but only paroxetine and sertraline have received FDA approval for use in PTSD. A few controlled studies have examined the efficacy of anticonvulsant [138] and antipsychotic monotherapy in the treatment of PTSD [139], and some authors [140] have suggested the potential efficacy of lamotrigine in PTSD.

If a patient does not respond to treatment with an SSRI or another antidepressant, an augmentation strategy with an antipsychotic should be attempted; two controlled trials have identified the efficacy of adjunctive risperidone and olanzapine with SSRIs [141].

FUTURE DEVELOPMENTS IN THE PSYCHOPHARMACOLOGY OF ANXIETY DISORDERS

A modern formulation of anxiety disorders involves the integration of several elements: life event stressors, the individual personality, the social supports available, and genetic vulnerability.

While this view is appropriate for anxiety syndromes in general, it does not apply to OCD. In fact, although its pathophysiology remains unclear, emerging evidence from distinct neurobiological studies indicate a predominantly biological nature of OCD, as Janet and Freud have hypothesized in the last century. A sequential approach, based on the use of pharmacotherapy in the acute phase and CBT ultimately, when the efficacy of the drug allows the patient to talk about himself or herself, is now broadly applied to treat anxiety disorders other than depression.

New targets and new drugs have been recently studied; however, the most interesting developments concern OCD and GAD.

Obsessive compulsive disorder

About 40-60% of patients affected by OCD do not respond to pharmacological treatment with an SSRI and with clomipramine, drugs considered the gold standard treatment for OCD. In about 30% of refractory OCD patients who do not respond to the above treatments, switching strategies can elicit an improvement in OCD symptoms. Clinical improvement can also be achieved by adding drugs acting on the dopaminergic system (typical and atypical antipsychotic drugs).

Clinical and experimental findings suggest that OCD is associated with an abnormality of the cortico-striato-pallido-thalamo-cortical circuits [27, 142] and that OCD symptoms are attributable to abnormalities in several limbic and cortical circuits.

The direct basal ganglia-thalamocortical pathway consists of two successive connections: from the striatum to the internal pallidum and from the internal pallidum to the thalamus, the indirect pathway includes an extra excitatory path from the subthalamic nucleus to the internal pallidum. In OCD the relative weakness of the indirect pathway impedes the termination of a behavioural programme thus making it difficult for a person with OCD to switch behavioural programme. By postulating generally hyperactive prefrontal glutamate neurones in OCD, we can understand also the behavioural inhibition, manifested as an over-cautious attitude and slowness.

Although the exact mechanisms are unknown, several studies have suggested that in OCD, there is a glutamatergic dysfunction with hyperactivity of the glutamatergic neurons in the prefrontal cortex [143-145]. Abnormalities in glutamate neurotransmission may include changes in the presynaptic release of glutamate, impaired clearance of synaptic glutamate by glial cells, or abnormalities in postsynaptic glutamate receptor expression or function [145].

Following the hypothesis of a glutamatergic abnormality, it has been shown that glutamatergic drugs such as riluzole, N-acetylcysteine (NAC), D-cycloserine, memantine, glycine, and nicotine can ameliorate clinical OCD symptoms. It is already known that [146, 147] riluzole produces beneficial effects in the treatment of patients affected by major depression, bipolar disorders, and anxiety disorders. An open-label study [148] conducted on 13 patients with refractory OCD and previously treated with SSRIs for 8 weeks demonstrated a significant decrease in the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) total score when riluzole was added to the SSRI treatment (augmentation). A recent

12-week open-label trial [149] on six patients (ages 8-16 years) affected by refractory OCD also demonstrated the efficacy of riluzole. Another drug that has been studied is NAC, an amino acid derivative commonly used for its hepatoprotective antioxidant properties; it can also, however, modulate brain glutamate neurotransmission. In a case report [150], NAC in augmentation to fluvoxamine produced a clear improvement in OCD symptoms. D-cycloserine is a glutamatergic partial agonist acting at the N-methyl D-aspartate (NMDA) receptor. A recent controlled study [151] demonstrated that D-cycloserine is effective for OCD refractory patients. Two case reports [152, 153] addressed the efficacy and tolerability of memantine, an antagonist of the NMDA receptor, in OCD patients, but the results are controversial. A recent open label trial [154] involving 15 OCD refractory patients, previously treated with a SSRIs, evidenced the efficacy and the tolerability of memantine (20 mg/dl) for 12 weeks; the authors proved that almost half the subjects had a meaningful improvement in OCD symptoms. Recently Feusner *et al*. [155] in an open label trial compared the efficacy and safety of 20 mg of memantine for 12 weeks in 10 OCD patients and 7 GAD patients. The results suggested that memantine may have preferential efficacy in the treatment of OCD versus GAD. One recent double-blind trial involving 24 OCD patients assessed the efficacy of glycine (60 g/day), an NMDA glutamate receptor agonist, finding that glycine given in augmentation could improve OCD symptoms [156].

Increased activity of sex steroid hormones [157] is thought to be present in OCD patients; thus, drugs acting as sex steroid antagonists have been used in the treatment of refractory OCD. Eriksonn [158] reported on one patient affected by resistant OCD treated with cyproterone acetate and demonstrating a significant improvement in symptoms. An open-label study conducted [159] with the same drug with eight patients who had refractory OCD demonstrated partial symptom improvement, although after 3-6 months of treatment, OCD symptoms re-emerged. Subsequently, other drugs acting on sex steroids, such as spironolactone, testolactone, aminoglutethimide, and oxytocin [160], have been investigated; however, the results are controversial and no firm conclusion can be reached. Controlled studies [161] have investigated the role of oxytocin in the treatment of patients with refractory OCD. A double-blind controlled study [162] has been carried out with 12 patients, nine females and three males, with 18 IU/day of oxytocin or placebo for two groups of patients, respectively, and no difference was noted between the groups. Finally, Epperson has conducted a controlled study with elevated doses of oxytocin (320 IU/day) in seven patients for 7 days and found no clinical benefit [163].

Other augmentation strategies, such as the use of amphetamines, stimulants of the central nervous system, have been proposed for the treatment of OCD. In a double-blind study [164], the authors tested the effect of d-amphetamine in comparison to a placebo in 12 patients affected by refractory OCD and observed an improvement in the obsessive symptoms. Nicotine is another compound that interacts with various neurotransmitter systems and that could have some beneficial effect on OCD symptoms. Few studies explained the prevalence of smoking among OCD patiens: one study [165] on 22 OCD patients demonstrated that only 2 of this patients were smokers; another study [166] on 83 subjects underlined a strikingly low prevalence of smoking among OCD patients compared with the general population and with non-OCD anxiety disorder patients. A controlled study [167] investigated the efficacy of nicotine (17.5 mg/day of nicotine for five consecutive days) on 11 non-smoking patients affected by OCD. The authors reported a decrease in the Y-BOCS total score and in particular of the compulsive partial score. Two case reports [168, 169] have shown that the administration of nicotine chewing gum in addition to standard treatment produced a reduction in the Y-BOCS total score and a decrease in the intensity and frequency of obsessions and compulsions. Lundberg [170] noted that patients previously treated with cognitive-behavioral psychotherapy responded better in comparison to patients refractory to SSRI treatment when nicotine was added.

After the demonstration of the efficacy of inositol, an isomer of glucose, in the treatment of depression and panic attack [171], Fux [172] performed a controlled study to estimate the drug effectiveness in OCD refractory patients. The author administered either 18 mg/day of inositol or placebo to two groups of patients, respectively, for 6 weeks. At follow-up, the patients in the inositol treatment group exhibited a reduction in symptomatology as scored with the Y-BOCS, but the placebo group patients did not. Recently, an open-label study [173] involving 12 patients with refractory OCD found that eight of these patients were responsive to treatment with 12 mg/day of inositol.

Another drug considered efficacious in the treatment of refractory OCD is ondansetron. This drug is an antagonist of the 5-HT3 serotoninergic receptor, and it is approved for the treatment of nausea induced by anti-neoplastic drugs. Hewlett [174], in an open-label study involving eight patients, demonstrated that ondasetron (3 mg/day) for 8 weeks had already proven effective during the second week of treatment.

The results on the efficacy of *Hypericum perforatum*, which inhibits the reuptake of serotonin, dopamine, and noradrenaline in the cerebral synapses, are controversial [175-177].

Few studies have evaluated the efficacy of lithium, which modulates serotoninergic, noradrenergic, and dopaminergic transmission, in the treatment of refractory OCD. Similar results have been obtained by Pigott [178] in a trial of 4 weeks, and by McDougle [179] when lithium was added to fluvoxamine. Although the use of lithium as a strategy of augmentation in OCD

patients with a depression comorbidity can be considered, the risk of serotoninergic syndrome should also be taken into account.

Preclinical studies have suggested that chronic treatments with SSRI can alter several markers of the opioid system [180]. In patients affected by OCD and Tourette Syndrome, some authors have discovered elevated antibody concentrations of anti-dynorfin in the serum [181]. In a double-blind controlled trial [182], naloxone, an opioid antagonist, worsened obsessive symptoms. Tramadol, another drug acting on the opioid pathways, has been investigated in patients with OCD [183, 184], with results suggesting that combined SSRIs and opioid-acting compounds can have efficacy in the treatment of refractory OCD.

A controlled trial [185] involving 23 patients showed the efficacy of morphine given orally for a week in improving OCDs. Recently, a trial carried out by Rojas Corrales [186] indicated that augmentation with an opioid agonist, typical or atypical, produces an improvement in OCD symptoms.

General anxiety disorder

Buspirone was approved for the treatment of GAD more than 20 years ago. In recent years, multiple members of the azapirone class, which comprises the partial or full 5-HTIA agonists gepirone, zalospirone, and ipsapirone, have been studied. These molecules show anxiolytic properties but have limitations in terms of tolerability. In a recent brief report, Mathew *et al*. [187] tested the short-term tolerability and efficacy of PRX-00023, a nonazapirone 5-HTIA selective partial agonist, in 23 outpatients with GAD. After the administration of PRX-00023 40 mg (days 1-4), 80 mg (days 5-14), and 120 mg (days 15-28), the authors investigated first the tolerability and second the outcomes, including the baseline-to-endpoint change in HAM-A (Hamilton Anxiety Rating Scale) total score, percentage meeting remission (HAM-A <7), and response criteria. This preliminary study indicated that PRX-00023 appeared to be generally well tolerated in patients with GAD. The primary efficacy measure was the HAM-A score at endpoint.

A glutamatergic dysfunction has also been postulated for the pathogenesis of GAD. In an open-label trial [188] on 18 patients with GAD, Mathew *et al*., investigated the efficacy and safety of treatment with riluzole (100 mg/day): of the 15 patients who completed the trial, 12 had a rapid improvement of anxiety symptomatology. Recently, Mathew *et al*. [189], in an open-label trial, used proton magnetic resonance spectroscopic imaging (1H MRSI) to examine the effects of the glutamate-release inhibitor riluzole on hippocampal N-acetylaspartate (NAA), a neuronal marker, in 14 patients with GAD. Moreover, the authors studied the relationship between NAA and the clinical outcome. From this work, they demonstrated a relationship between hippocampal NAA and symptom alleviation after the administration of riluzole in patients for 8 weeks; this result suggested that riluzole might be efficacious for GAD (and subtypes of mood disorders) in part because of reduced glutamate excitotoxicity and enhancement of hippocampal neuroplasticity.

Valproate is another drug that has been investigated for the management of GAD in a double-blind, placebo-controlled randomized trial involving 80 male patients [190]. Each patient was randomized to receive either depakine-chrono (40 patients), 500 mg three times per day for 6 weeks, or matched placebo (40 patients) in a double-blind manner. The patients were evaluated by HAM-A at 4 and 6 weeks. The authors demonstrated that 26 out of the 36 depakine-chrono-treated participants responded by 6 weeks, versus 6 of the 38 placebo-treated participants; in addition, the most common side effects in the depakine-chrono group were dizziness and nausea.

CONCLUSION

In this review, we have outlined studies that have demonstrated improvement in symptoms of anxiety disorders. Given the available data, SSRIs and SNRIs are beneficial therapeutic agents for PD, GAD, and PTSD, and partially for OCD. Other drugs, such as pregabalin, have been shown to alleviate anxiety symptoms. The efficacy of these drugs has fortunately decreased the misuse of benzodiazepines; however, self-prescribing is still common. Functional neuroimaging studies have focused on specific cerebral structures as targets for specific drugs; examples include the amygdala and the anterior insula for GAD, or the CSTC for OCD. Furthermore, researchers have identified several intracellular mechanisms of action of SSRIs that might explain their long-term efficacy. Further research in larger populations is warranted to test the potential role of glutamatergic systems in the treatment of anxiety symptoms and OCD.

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