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Off-label uses of trazodone: a review

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Introduction: Trazodone is an antidepressant belonging to the class of serotonin receptor antagonists and reuptake inhibitors. It is approved by the FDA for the treatment of depression. Insomnia is the most frequent reason for prescription of trazodone. It has also been proven useful in the treatment of anxiety disorders. Other off-label uses include the treatment of bulimia, benzodiazepine/alcohol dependence, fibromyalgia, central nervous system degenerative diseases (behavioral disorders in dementia and other organic disorders), schizophrenia, chronic pain disease and diabetic neuropathy, sexual dysfunction.

Areas covered: This paper evaluates trazodone's efficacy and safety in its off-label uses. It also discusses the possibility that a combination of trazodone with SSRIs may prevent or treat some of the SSRI side effects, such as anxiety, insomnia and sexual dysfunction, in addition to synergically increasing SSRIs' antidepressant activity.

Expert opinion: Few clinical trials have been conducted to evaluate trazodone's efficacy in the treatment of the diseases and symptoms for which it is often used in clinical practice. More studies are necessary to investigate possible new therapeutic indications, and to scientifically demonstrate the risk/benefit ratio for the many conditions for which trazodone is used, but not approved by the FDA.

Keywords: acceleration, augmentation, off-label uses, trazodone

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1. Introduction

Trazodone, a triazolopyridine derivative, was first synthesized in the '70s and still represents a therapeutic option for depressive disorders with or without an anxiety component. It behaves as an antagonist of serotonin type 2 (5-HT2) and alpha1-adrenergic receptors, and as an inhibitor of 5-HT reuptake (Serotonin Antagonist-Reuptake Inhibitors, SARI), representing the prototype of this group of drugs [1]. Trazodone is characterized by a moderate antihistaminic activity and low anticholinergic and dopaminergic activity [1]. Despite its existence for nearly 40 years, its mechanism of action continues to be at least partially unknown.

The main pharmacological property of trazodone is its antagonism of the receptor for serotonin 5-HT2A (1 mg of trazodone will occupy about half of 5HT2A receptors) [1]. At higher doses (50 mg), the antagonism also affects alpha 1-adrenergic, histamine H1 and alpha 2 receptors [1]. Trazodone's ability to block SERT (serotonin transporter) is at least 100 times less potent than its ability to block the 5-HT2A receptor [1]. The action on 5-HT2A, alpha 1 and H1 receptors is considered the basis for the drug's hypnotic effect [1] at low doses (25–100 mg), whereas the simultaneous blocking of 5-HT2A and SERT is required for its antidepressant effect [1], which occurs at higher doses (150–600 mg).

The combined action of 5-HT2A antagonism and SERT blocking leads to positive clinical implications in terms of tolerability [1]. In the past, it was assumed that only

Article highlights.

- Trazodone is approved by the FDA for the treatment of major depressive disorder, but it is frequently used off-label. The off-label use of the drug for insomnia, whether primary or secondary, is currently the most frequent reason for prescription of trazodone.
- Trazodone has also been proven useful in the treatment of anxiety disorders, such as Generalized Anxiety Disorder, Panic Disorder, Post-Traumatic Stress Disorder and Obsessive-Compulsive Disorder. Other, not officially approved, uses of trazodone include the treatment of: bulimia, benzodiazepine and alcohol dependence and/or abuse, fibromyalgia, central nervous system degenerative diseases such as behavioral disorders in dementia and other organic disorders, schizophrenia, chronic pain disease, diabetic neuropathy and sexual dysfunction.
- Thanks to its 5-HT2A receptor antagonism, trazodone has been demonstrated capable of preventing the occurrence of initial and long-term side effects of SSRIs, in particular anxiety, insomnia and sexual dysfunction.
- Moreover, pharmacological characteristics of the drug clearly suggest the possibility of a synergistic antidepressant action, as well as an increased tolerability, in the case of association between trazodone and SSRI drugs. Despite the interesting hypotheses derived from pharmacodynamic theory, at present there are no studies in the literature to provide the necessary empirical data.

This box summarizes key points contained in the article.

the 5-HT2A antagonism was sufficient to induce sleep. However, although 10 mg of trazodone are sufficient to saturate almost 100% of 5-HT2A receptors, its hypnotic effect appears only at higher doses, which suggests that the drug also acts on alpha 1 and H1 receptors: at these doses, the drug induces and maintains physiological sleep, without causing addiction or residual sedation in the morning, due to its short half-life of 3–6 hours [1]. Trazodone is converted by CYP3A4 into an active metabolite known as meta-chloro-phenyl piperazine (mCPP). This agent has high affinity for a number of serotonin receptors, including 5HT2C > 5HT2A; it functions as an agonist, whereas trazodone acts as an antagonist. These pharmacologic actions of mCPP may contribute to the net effects of trazodone and could probably mitigate trazodone's antagonism on 5-HT2A and 5-HT2C receptors. However, plasma and brain levels of mCPP appear to be less than 10% of those of trazodone. Thus, the antagonist action of trazodone appears to overwhelm any effects of mCPP and blocks any agonism mCPP might have on 5HT2A and 5-HT2C receptors. Possible interactions between mCPP and other drugs metabolized by CYP3A4 may alterate trazodone pharmacologic effect [1].

1.1 Trazodone in depression

Trazodone was approved by the FDA for the treatment of Major Depressive Disorder (MDD) on December 24, 1981. However, despite the efficacy data emerging from the literature, trazodone has always shown low effectiveness in clinical practice. The first data on the trazodone as an antidepressant date back to a systematic clinical study performed in the '70s [2], which evaluated its therapeutic activity in depressive disorders, as well as in relation to depressive symptoms in the course of other psychiatric (neuroses, psychoses) and organic disorders.

A second clinical study [3] confirmed the antidepressant and anxiolytic effect of low-dose trazodone and the absence of significant side effects, due to a hypothetical anti-serotonin activity suggested by a decreased excretion of 5HIAA in 24-hour urine. The positive therapeutic effects of trazodone against endogenous depression and the absence of significant adverse effects were confirmed by a further double-blind study [4], in which trazodone was found to be superior to imipramine and placebo.

During the '80s, there was a significant upsurge in interest in trazodone. Many studies compared it with tricyclic antidepressants such as imipramine, desipramine and amitriptyline [5,6], and demonstrated the comparable antidepressant effect of trazodone, which was sometimes less powerful but more selective on the serotonin system at low doses, and which lacked the anticholinergic side effects typical of this class of drugs. Due to the low incidence of neurological side effects, trazodone was also shown to be a valuable therapeutic tool in the elderly. It was also found to have a useful therapeutic effect against the anxiety component in depressed patients [7-9].

From the late '80s, trazodone was compared with the new SSRIs such as fluoxetine, demonstrating a greater effect on depressive symptoms (assessed by the HAM-D) in the first 3 weeks of treatment as well as a better effect on sleep [10]. However, after the first 3 weeks of treatment, fluoxetine was superior to trazodone in inducing the remission of depressive disorders, suggesting that SSRIs simply took longer to establish their therapeutic effect [11].

Interest in trazodone continued into the '90s [12,13] when, having been found comparable in effectiveness to tricyclic antidepressants, as well as to fluoxetine and mianserin, it was proposed as a possible first-line therapy against depression in the elderly and was even considered safe for use in patients suffering from heart disease. However, pending further confirmatory clinical studies, it was suggested that trazodone be reserved for patients who do not respond to or cannot tolerate other drugs, or to those with contraindications to electroconvulsive therapy [14-16].

In 1992, a possible potentiating effect of trazodone in combination with fluoxetine was noticed, but this study remained isolated and further research was not carried out, possibly to avoid a serotonin syndrome induced by this pharmacological combination [17].

In the first decade of the new century, research continued to be carried out on trazodone as an antidepressant agent. Recent studies have focused on comparisons between trazodone and other classes of drugs (SSRIs, SNRIs) and on pharmacological combinations including trazodone, in order to exploit its

protective effect against troublesome SSRI-induced adverse effects, such as sexual dysfunction [18,19]. Compared to venlafaxine, trazodone has demonstrated equal antidepressant efficacy, with a more rapid onset of therapeutic effect [20]; compared to sertraline and paroxetine, which have the same antidepressant effect, trazodone seems to be advisable for depressed patients with sleep disorders [21,22]. Data from a 2007 meta-analysis confirm that trazodone and SSRIs do not differ in terms of efficacy and tolerability in the treatment of depressive disorders [23]. A further study has confirmed the efficacy of trazodone compared to placebo in relation to depressive disorders, its ability to improve mood by reducing feelings of guilt and suicidal ideation, and its positive effect on anxiety and sleep [24].

In the last two years, a few studies have focused on the use of trazodone in depressive disorders [25], suggesting the use of sustained-release formulations [26] rather than immediate release ones, which have good potential as hypnotics and the ability to prevent nightmares in MDD [27].

1.2 Adverse effects

The most common adverse effects of trazodone include daytime sleepiness and excessive sedation [28], headache, dizziness and hypotension [28]. There have been reports of priapism (as in the case of other adrenolytic drugs), with increased libido and extension of nocturnal erections in clinical practice, which is one of the reasons for trazodone being considered effective in the treatment of sexual dysfunction [29]. Patients at high risk for the development of priapism include those with sickle cell anemia or sickle cell trait, leukemia, autonomic nervous system dysfunctions or hypercoagulable states. In addition, high-risk patients include those taking SSRIs (dose-related) and those using cocaine or who have overdosed on cocaine or trazodone. Because of their predisposition to this serious complication of trazodone, these patients should be treated cautiously and alternative therapeutic strategies should be considered for the treatment of insomnia or depression [30].

The occurrence of gastric distress, nausea, vomiting and decreased appetite has rarely been reported [30]. Trazodone presents minimal anticholinergic features, so it is generally considered to have less cardiotoxic potential than other antidepressant drugs. Nevertheless, a report describes a young woman who developed significant QT prolongation and delayed atrioventricular nodal conduction after acute trazodone overdose. It is necessary to consider the possibility of cardiotoxic effects after trazodone overdose, even in young patients with no established cardiovascular disease [31]. Postural hypotension is the most described cardiovascular adverse effect; this is much less likely to appear if the drug is taken with meals. There have repeatedly been reports of cardiac arrhythmias associated with trazodone, due to the blockade of adrenergic receptors and consequent prolonged QTc [28], so concerns have been raised regarding the cardiac safety of trazodone. Rare ventricular ectopies, including ventricular tachycardia, have been described during treatment with trazodone. Interactions with HERG potassium channels seem to be the main factor of cardiac adverse effects: trazodone blocks cardiac HERG channels at concentrations that are probably relevant *in vivo*, particularly in overdosage [32]. In a case study, after a single dose of trazodone, a patient developed complete heart block [33]. Despite the results of earlier studies, trazodone's effect on cardiac conduction may be severe in individuals at risk for conduction delay.

2. Off-label uses

As trazodone is frequently used off-label, we conducted a review to assess the safety and tolerability of this drug in the most common off-label uses. We analyzed the scientific material available on PubMed concerning the possible clinical uses of trazodone. Specifically, we searched for articles published between 1970 and 2012, using the following terms: trazodone, depression, insomnia, anxiety (then Generalized Anxiety Disorder, Post-Traumatic Stress Disorder, Obsessive-Compulsive Disorder and Panic Disorder), off-label uses (then bulimia, benzodiazepine abuse, alcohol withdrawal, fibromyalgia, dementia, schizophrenia and chronic pain, sexual disorders) and SSRIs combination. We examined all the articles available, making a distinction between randomized placebo-controlled trials, clinical trials, meta-analysis, case reports and reviews; no inclusion/exclusion criteria were considered, no language restriction was placed on the literature search.

Many psychiatric and non-psychiatric disorders are included among the possible clinical uses of trazodone. Although its only FDA-approved use is for depressive disorders with or without an anxiety component, in most cases the drug is used for off-label purposes.

2.1 Insomnia

The most frequent reason for the prescription of trazodone is currently its off-label use against insomnia, whether primary or secondary [1]. Although trazodone is widely used to treat insomnia in general population, the most studied subjects in literature resulted to be the elderly [34,35].

Due to its anxiolytic action and its effect on the normalization of sleep in depression, trazodone is widely used in the place of benzodiazepines, in an attempt to exploit its sedative action without the risk of addiction and dependence typical of other hypnotic drugs [24]. Although widespread in the general population, insomnia is an underestimated and underdiagnosed condition. Similarly, despite being the most frequent symptoms patients complain of in old age (over 65), sleep disorders are rarely diagnosed or treated by specialists in geriatrics [34,35].

Insomnia is a serious problem, not only because of its high incidence, but also due to its harmful consequences on many aspects of sufferers' lives. In particular, sleep disorders in the elderly population are associated with a significant increase in morbidity and mortality and with an increase in admission to nursing homes [34].

The continuity of sleep, rather than difficulty in getting to sleep, is the most commonly complained about problem among elderly people with sleep disorders [36]. Despite a range of treatment options being available, there is still a lack of pharmacological agents capable of providing an optimal combination of therapeutic effects and tolerability, that is, improving sleep onset and continuity without any residual effects the following day, or effects on cognitive functioning in the elderly [35]. Benzodiazepines and antidepressants, such as trazodone, are the most commonly prescribed drug categories for insomnia in elderly patients.

Many studies have evaluated the antidepressant effectiveness of trazodone in the elderly, yet there is little information about its use in the treatment of insomnia in this population.

The first data in the literature concerning the use of trazodone for the treatment of insomnia date back to two studies carried out in the '80s [37,38]. Interest in the hypnotic effect of trazodone increased significantly in the '90s, when its effectiveness emerged with regard both to patients suffering from primary insomnia [12] and to those suffering from insomnia associated with a depressive state [16,39,40].

Moreover, in recent years the sedative effect of trazodone has been compared with fluoxetine: a preliminary study noted the same effectiveness between the two drugs [41], whereas a second study of 1997 showed a slight superiority of trazodone compared to fluoxetine in relieving the symptoms of insomnia in depressed patients [42].

Finally, studies have shown a good sedative effect of trazodone in depressed patients treated with MAOIs [43].

Over the last 10 years, the efficacy of trazodone in the treatment of insomnia has been demonstrated repeatedly–in its primary form [44], when it is a symptom of depression [45] and, finally, when associated with dementia [46], or anxiety disorders such as PTSD [47] or other psychiatric and/or non-psychiatric disorders.

In summary, over the years trazodone has been a valuable tool in the treatment of insomnia. It should be stressed, however, that the data in the literature are limited, especially concerning primary insomnia; the clinical trials are short (never more than six weeks), and objective measures of its effectiveness in support of empirical observations are lacking [48].

Further reservations about the widespread use of trazodone to treat insomnia result from its potentially serious side effects, including residual daytime sedation, dizziness, orthostatic hypotension, psychomotor impairment and priapism [35], as well as the possibility of establishing tolerance, especially after 1–2 weeks [48]. These factors raise doubts about the safe use of this drug in the elderly and are probably the reason why the use of trazodone in the treatment of insomnia is currently off-label in many countries, not yet having received official approval.

2.2 Anxiety

It is well known that both pharmacological and psychotherapeutic approaches can be beneficial in the treatment of anxiety disorders. As regards drug therapies, few different strategies are available and they are mainly represented by two classes of drugs: benzodiazepines and antidepressants. Benzodiazepines have anxiolytic and hypnotic properties and are fast in controlling clinical symptoms, but inappropriate because of their reduced efficacy in the long term. This is probably due to the fact that GABA is not the only neurotransmitter to be involved, but serotonin and norepinephrine may also play a decisive role. This is the rationale for the use of antidepressants in the treatment of anxiety disorders, especially drugs that show significant effects in the long term, unlike benzodiazepines.

Over the years, a number of studies have tested the efficacy and safety of various classes of antidepressants in several clinical syndromes. Trazodone has also been the subject of such research and proved to be a viable treatment option.

Antidepressants are the treatment of first choice in Generalized Anxiety Disorder, in both the presence and absence of a major depressive episode. Trazodone has also been proven useful in the treatment of this disorder [49], with an efficacy comparable to that of imipramine and diazepam [50].

The efficacy of trazodone in treating Panic Disorder has not been confirmed. In some cases it seems to be ineffective, even poorly tolerated [51], whereas in others it seems to be associated with significant improvements in all clinical manifestations of the disorder, such as generalized anxiety, phobias, depression and avoidance conduct, with a specific anti-panic and anti-phobic effect [52].

In Post-Traumatic Stress Disorder (PTSD), SSRIs are the treatment of first choice, but when these are not tolerated or ineffective, the second-line treatment is represented by non-serotonergic drugs such as trazodone, with a significant improvement in social and occupational functioning [53]. Very high percentages (70–91%) of sleep disturbances are shown to be in association with PTSD and particular difficulty in initiating and maintaining sleep [54]. SSRIs have a modest effect on these disorders, whereas trazodone leads to a significant reduction of insomnia. Out of 60 subjects in a 2001 study on the usefulness of trazodone in the treatment of insomnia and nightmares in patients with PTSD [47], 72% reported a decrease in nightmares, 92% found less difficulty in initiating sleep and 78% showed improvements in sleep maintenance.

Regarding Obsessive-Compulsive Disorder, with rare exceptions [55] in which no substantial difference in efficacy between trazodone and placebo was found, the literature is generally unanimous in believing trazodone to be a useful drug in the treatment of this disorder [56], although with only mild improvements [57]. In some cases, not only the clinical efficacy of trazodone, but also its ability to reduce SSRI-induced side effects were demonstrated [58].

2.3 Further off-label uses

Other, not officially approved, uses of trazodone concern the treatment of: bulimia [59], benzodiazepine and alcohol

dependence and abuse [25], fibromyalgia [60], central nervous system degenerative diseases such as dementia and other organic disorders [25,61], schizophrenia [19], chronic pain disease [25], diabetic neuropathy [62] and sexual dysfunction [19].

2.3.1 Bulimia

Antidepressants have long been used in the treatment of bulimia and no real differences in efficacy and tolerability have been found among the various classes [63]. Their effectiveness has been proven in bulimic patients without concomitant depressive symptoms. Trazodone, in particular, is well tolerated and effective in reducing the number of binge eating and vomiting episodes, compared to placebo [64,65].

2.3.2 Benzodiazepine abuse

Dependence on such drugs is a very common problem. The goal of treatment in these patients should be to avoid relapse. The first-line treatment for addiction problems ought to be non-pharmacological, but when this is not possible, physicians should avoid drugs with a potential for abuse or dependence. Benzodiazepines are a class of drugs with a broad spectrum of activity, rapid onset of action and a wide therapeutic range compared to other substances with an anxiolytic action. However, their use is limited by the fact that they can induce dependence and abuse [66]. A 1993 study showed the usefulness of trazodone as an alternative to benzodiazepines in patients suffering from anxiety symptoms who were at risk of abuse [67].

2.3.3 Sleep disturbances in alcohol withdrawal syndrome

The off-label use of trazodone in the treatment of alcohol withdrawal syndrome was already suggested in the '80s [68] and '90s [69]; in these cases the drug was shown to be useful in promoting abstinence and reducing the desire for alcohol. Since 2003, research has shown a growing interest in this topic. Sleep disorders are common among patients with alcohol withdrawal; a proper management of sleep is of paramount importance in these patients, especially in the early stages, as these difficulties are considered responsible for many cases of relapse [70]. Trazodone is the most commonly used drug for this purpose, as it presents less risk of addiction and abuse than benzodiazepines [71]. In 2003, a postal survey was conducted [72] on a sample of 503 members of the American Society of Addiction Medicine (ASAM), to assess the way ASAM doctors managed sleep disorders in patients in early recovery from alcoholism. Only 62% of the physicians contacted responded to the survey, but 64% of these recommended pharmacological treatment to their patients: trazodone was found to be the most widely used drug, despite the scarce clinical evidence to support this use. Beyond these purely empirical data, a 2008 study [71] seems to question the safety of trazodone therapy in patients at high risk of relapse. Although this study reaffirmed the efficacy of trazodone in improving patients' quality of sleep during the treatment period, at the end of the therapy the quality of sleep matched that of patients under placebo; moreover, the drug seemed to undermine patients' progress in terms of days of abstinence during the period of treatment, and to produce an increase in the number of drinks per day at the end of therapy. For these reasons, despite the limited evidence, trazodone therapy cannot be recommended with sufficient certainty for the treatment of sleep disturbances during alcohol detoxification.

2.3.4 Fibromyalgia

The usefulness of trazodone in the treatment of fibromyalgia (although at higher doses than usually prescribed) goes beyond its role as a hypnotic agent. According to a recent study, in fact, not only does trazodone improve the quality of sleep in these patients, it also has a significant effect on fibromyalgia symptoms, as measured by the Fibromyalgia Impact Questionnaire (FIQ) [60]. Trazodone has also been found to significantly improve the severity of fibromyalgia and associated symptoms (sleep quality, depression and pain interfering with daily activities); these improvements are greatly enhanced by association with pregabalin [73].

2.3.5 Behavioral disorders in dementia

Since the '80s, the off-label use of trazodone has been suggested in the treatment of behavioral disorders (irritability, anxiety, verbal aggression) associated with various forms of dementia. However, the literature on this topic offers ambiguous conclusions. In the '80s and the '90s trazodone was judged positively, although with some exceptions despite a clear need for confirmation in double-blind placebo-controlled studies [74], and it was even recommended as an alternative to neuroleptics [75,76]. In the late '90s, however, this enthusiasm was dampened by a study comparing the efficacy and side effects of trazodone and haloperidol; no significant difference was shown in terms of their effectiveness, but side effects were most common in the group of patients treated with haloperidol [77]. In the last decade, albeit with some exceptions [78], researchers have been more cautious: in some cases they have suggested the effectiveness of trazodone for only some of the Behavioral and Psychological Symptoms of Dementia (BPSD) associated with Alzheimer's disease, such as aggression and negativism in caregiving situations [79]; in other cases they have claimed that patients did not show any improvement in BPSD after 6 months of treatment with trazodone [61], thus essentially negating any real effect; and, last, others have questioned whether the drug has any clinical efficacy at all, as a comparison with placebo did not show significant benefits [80]. More recently, trazodone has been judged as an excellent therapeutic option in elderly patients with dementia associated with sleep disorders [46], confirming that the drug exhibits its greatest efficacy in its use as a hypnotic.

2.3.6 Schizophrenia

Serotoninergic antidepressants, used in combination with neuroleptics, are safe and effective in the treatment of negative

symptoms in elderly patients with chronic schizophrenia [81]. More precisely, trazodone significantly reduces the severity of negative symptoms without increasing the positive ones, although the extent of the therapeutic effect remains modest [82].

2.3.7 *Acute neuroleptic-induced akathisia*

Akathisia is a common and distressful extrapyramidal side effect usually resulting from the use of antipsychotic medications. Many patients fail to respond to standard management of akathisia. Despite the high incidence of this disorder, its mechanism of action has not yet been adequately explained: in addition to dopaminergic mechanisms, it has been hypothesized that serotonin may play a prominent role in the pathophysiology of akathisia. Trazodone is an antidepressant agent demonstrating principal serotonergic antagonistic features and, according to recent studies, it has been demonstrated effective in the treatment of neuroleptic-induced acute akathisia; it seems that trazodone clinical efficacy, in this case, is related to its postsynaptic 5-HT2A receptor antagonism [83].

Mirtazapine seems to be an effective anti-akathisia compound at low doses, due to its marked 5-HT2A antagonism. However, higher doses of the drug have been proven to be associated with akathisia onset in susceptible individuals, probably due to the stimulation of adrenergic neurotransmission via alpha2 auto-receptor blockade. It seems that mirtazapine is unique in its dose-related bidirectional effect on akathisia: low doses have an anti-akathisia effect, higher doses may instead induce akathisia [84]. The antidepressant mianserin, that shares marked 5-HT2A antagonism at low doses with trazodone, revealed anti-akathisia characteristics in antipsychotic-treated schizophrenia patients [85]. Notably, the effect of low-dose mianserin and mirtazapine on antipsychotic-induced parkinsonism does not significantly differ from that of placebo, supporting the hypothesis that distinct pharmacological mechanisms underlie antipsychotic-induced extrapyramidal side effects [86]. Nefazodone blocks postsynaptic 5HT2A receptors and weakly inhibits serotonin reuptake; it has been proven to have a therapeutic role in the treatment of antipsychotic-induced akathisia [87].

Trazodone, mirtazapine, mianserin and nefazodone share, indeed, serotonergic antagonistic properties, effective in the treatment of neuroleptic-induced acute akathisia. No data in literature help to compare advantages and/or disadvantages between these drugs, so it is difficult to choose the most suitable among them for the treatment of acute akathisia.

2.3.8 *Chronic pain disorders*

Chronic pain, which many doctors are forced to deal with sooner or later, is difficult to resolve in clinical practice. According to some (rather dated) theories [88], serotonin may somehow be involved in the mechanism of action that leads to the onset of chronic pain. This has led to the idea that drugs which inhibit the reuptake of serotonin may be useful in this regard, prompting a steady interest in trazodone in relation to various pain syndromes. In the case of dysesthetic pain syndrome (DPS) [89], for example, no real efficacy of trazodone compared to placebo was demonstrated, whereas a significant number of patients assigned to the active drug group complained about the onset of side effects, which led them to leave the study prematurely. Even in the case of chronic low back pain syndrome [90] there were no significant differences between the group assigned to trazodone and those assigned to placebo. The same was true in the case of burning mouth syndrome [91] where trazodone completely failed to meet expectations of efficacy. The only case in which trazodone showed real efficacy towards a pain syndrome was in a 1999 study [62] in which it proved useful in the treatment of pain associated with diabetic neuropathy.

2.3.9 *Sexual disorders*

An unusual side effect of trazodone, priapism, has led researchers to evaluate the use of this drug in the treatment of erectile dysfunction. However, the literature on this topic is conflicting. Some studies assert that trazodone is no more effective than placebo in improving erections and sexual function, and that it may even be the cause for dysfunctions [92-94]. According to other authors, however, trazodone can be used as adjuvant therapy in the treatment of non-organic male sexual dysfunctions [29], although the improvement recorded was not statistically significant [95]. In a more recent study, trazodone was found to be effective, safe, fast-acting and to have few side effects in the treatment of sexual dysfunction [96,97]. Its effectiveness has also been demonstrated in the management of SSRI-induced sexual dysfunction [98], a problem which is often a cause of therapy discontinuation or of reduced compliance by the patient, resulting in failure of the treatment [19]. To date, the mechanism underlying SSRI-induced sexual dysfunctions remains incompletely understood. By raising serotonin at all serotonin receptors and in all brain areas, SERT inhibitors such as SSRIs simultaneously cause antidepressant actions by stimulating 5-HT1A receptors. Yet, they also cause adverse effects (such as sexual dysfunction) by stimulating 5-HT2A and 5-HT2C receptors. When SERT inhibition is combined with 5-HT2A and 5-HT2C inhibition—as it happens with trazodone—it is possible to obtain an antidepressant action without sexual disorders. It is therefore suggested that trazodone drug antagonism on serotonin receptors may improve sexual dysfunctions reverting the stimulation of those serotonin receptors by SSRIs [96]. Also, a beneficial effect may be due to trazodone antagonism at the peripheral α-adrenoceptors [1,97].

2.4 Combination with SSRIs

Thanks to its 5-HT2A receptor antagonism, trazodone has been demonstrated capable of preventing the occurrence of initial and long-term side effects of SSRIs, in particular, anxiety, insomnia and sexual dysfunction [1,19,99]. Moreover,

a theoretical rationale suggests the possibility of a synergistic antidepressant action, as well as an increased tolerability, in the case of association between trazodone and SSRI drugs [100]. A potential neurobiological basis for the augmentation effect of this association lies in the opposite action that serotonin exerts in the prefrontal cortex: neurons in this area are stimulated at the level of the 5-HT2A receptor and inhibited at the level of the 5-HT1A receptor; consequently, a balance between these two mechanisms results in no net effect (excitation or inhibition). Theoretically, in the course of depression, the pyramidal cells of the prefrontal cortex are hyperactive and the role of serotonergic antidepressants should be to inhibit these neurons via the 5-HT1A receptor. However, when serotonin levels increase, due to the block of SERT mediated by SSRIs, both 5-HT1A and 5-HT2A receptors are simultaneously stimulated, with no net effect on the neuron; when trazodone blocks 5-HT2A receptors while 5-HT1A receptors continue to be stimulated, both the inhibitory effect against the neuron and the consequent antidepressant effect are potentiated [1,17,99]. Another mechanism that could explain the synergistic effect between the 5-HT2A antagonism and SERT blockade can be found in an increased release of dopamine and norepinephrine in the prefrontal cortex [101]. The stimulation of serotonin 5-HT2A receptors inhibits the release of these neurotransmitters through a GABAergic mechanism; trazodone, blocking 5-HT2A receptors, would be able to uninhibit this release, thereby enhancing the antidepressant effect of SSRIs.

However, although many pharmacological characteristics of trazodone clearly suggest a potential synergistic action towards SSRIs, this remains purely theoretical. So far no clinical study has shown that the addition of a 5-HT2A antagonist to SSRIs is capable of enhancing their antidepressant effect. Nonetheless, it is undeniable that this notion is perfectly consistent with the observations that atypical antipsychotics, which have antagonistic effects on serotonin 5-HT2A receptors as a first level property (meaning that they have a higher affinity for these receptors), are able to enhance the response to SSRIs in some depressed patients, especially those with resistant depression [1]. As regards a possible association between trazodone and fluoxetine, the latter has no significant impact on trazodone serum levels, with no evidence of any of the side effects indicative of an interaction (dizziness, severe headache, daytime sedation, fatigue, serotonin syndrome even in a mild form) [102]. However, fluoxetine-induced increase in plasma mCPP concentrations can be observed, which may contribute to the clinical efficacy of the combination of fluoxetine with trazodone. It is suggested that desensitization of 5-HT2C receptor function by mCPP, as well as fluoxetine, may contribute to the antidepressant effect of this association [103].

Despite the interesting hypotheses derived from pharmacodynamic theory, at present there are no studies in the literature to provide the necessary empirical data.

3. Conclusions

This article set out to review the scientific literature on the many clinical uses of trazodone. From the previously reported data, it appears that trazodone may be considered a multifunctional drug. Generally approved for the treatment of major depression, its effectiveness has also been documented in elderly patients with insomnia.

Among its off-label uses, trazodone is well tolerated and effective in reducing the number of binge eating and vomiting episodes in bulimia and has been found to significantly improve the severity of fibromyalgia and associated symptoms (sleep quality, depression and pain interfering with daily activities). The usefulness of trazodone has been demonstrated in patients suffering from anxiety symptoms and at risk of benzodiazepine abuse, along with its efficacy in improving patients' quality of sleep in alcohol withdrawal; in the latter case, however, the drug seems to undermine patients' progress in terms of days of abstinence during the period of treatment and to produce an increase in the number of drinks per day at the end of therapy. Trazodone cannot therefore be recommended with sufficient certainty to treat sleep disturbances during alcohol detoxification. Studies on the off-label use of trazodone in the treatment of behavioral disorders associated with dementia have led to ambiguous conclusions, although it has recently been judged as an excellent therapeutic option in patients with dementia associated with sleep disorders. Trazodone's efficacy on the negative symptoms of schizophrenia remains modest, but it has been proven effective in the treatment of acute neuroleptic-induced akathisia, probably because of its postsynaptic 5-HT2A receptor antagonism. As regards chronic pain syndromes, the only case in which trazodone showed real efficacy towards a pain syndrome was in the treatment of pain associated with diabetic neuropathy. Trazodone has also been demonstrated effective in the management of SSRI-induced sexual dysfunction: these effects would be mainly due to its action on α-adrenoceptor antagonists.

4. Expert opinion

Considering the limitations due to the paucity of studies in the literature, which are also often conflicting, the need to improve research on trazodone, meant at overcoming this weakness in this field, is clear.

Particularly, it is necessary to stress on the fact that, among the few available studies on each disorder trazodone has been used for, randomized placebo-controlled trials represent an even small minority. This does not help to ensure adequate scientific evidence to justify the use of the drug in this large variety of diseases. Studies are needed to test the potential benefits of trazodone for augmentation and/or acceleration of the response to SSRIs, or the potential to reduce SSRIs-induced side effects.

Although off-label use should not be encouraged, the wide range of off-label applications may help to make this drug an interesting candidate for further research in the near future.

Avenues of research likely to become exciting as further studies could cover areas such as:

1) acceleration effect of trazodone: assessment of the time required for the establishment of a clinical response to the treatment with SSRIs in combination with trazodone;
2) effects on efficacy and augmentation effect on the response to SSRI;
3) evaluation of the ability of trazodone to reduce SSRIs-induced adverse effects.

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