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Off-Label Trazodone Prescription: Evidence, Benefits and Risks

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Abstract: Although trazodone is approved and marketed in most countries worldwide for the sole treatment of Major Depressive Disorder, the use for this medication is very common for many other conditions, such as primary or secondary insomnia, Generalised 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/or alcohol dependence or abuse, fibromyalgia, degenerative diseases of the central nervous system such as dementia and other organic disorders, schizophrenia, chronic pain, and diabetic neuropathy. In addition, due to its 5HT2A receptor antagonistic action, trazodone may be used to prevent the occurrence of initial and long-term side effects of SSRI, such as anxiety, insomnia and sexual dysfunction.

Despite the favorable clinical experience and the encouraging results from the studies that have tested the efficacy of trazodone for some of its off-label indications, it is paramount that large, randomized and controlled clinical trials be conducted in the near future to evaluate which of the many off-label indications are supported by a strong scientific evidence.

Keywords: Anxiety, insomnia, off label, SSRI combination, serotonergic, trazodone.

INTRODUCTION

Trazodone is a drug developed in the 70s and still represents a valid therapeutic option for depressive disorders with or without an anxiety component. Trazodone is a triazolopyridine derivative and acts as an antagonist of serotonin (5-HT) of type2 and of alpha1-adrenergic receptors, as well as an inhibitor of 5-HT reuptake. It is characterized by a moderate antihistaminic activity and has low anticholinergic and dopaminergic activity [1, 2]. As an antidepressant, it constitutes the prototype of the group of 5HT2 antagonists and serotonin reuptake inhibitors -SARI- [3]. In spite of the existence of this compound for nearly 40 years, its mechanism of action continues to be the subject of study and research.

The main pharmacological property of trazodone is the antagonism of the receptor for serotonin 5HT2A. By increasing the dose, the antagonist effect on the alpha 1-adrenergic, histamine H1 and alpha 2 receptors appears. The ability to block SERT (serotonin transporter) is at least 100 times less potent than blocking the 5HT2A receptor. The action on 5HT2A, alpha 1 and H1 receptors is considered the base of the hypnotic effect of low doses of trazodone (25-100 mg). At these doses the drug induces and maintains the physiological sleep without causing a residual sedation in the morning due to its short half-life -about 3-6 hours- [4, 5].

For its antidepressant effect simultaneous blocking of 5HT2A and SERT is required, a phenomenon that occurs at higher doses (150-600 mg).

The combined actions of 5HT2A antagonism and SERT blocking result in greater tolerance and have positive clinical implications. Previously, it was assumed that only the 5HT2A antagonism was sufficient to induce sleep. However, although 10 mg of trazodone is sufficient to saturate almost 100% of 5HT2A receptors, its effect as a hypnotic agent appears only at higher doses, necessary to ensure that the drug may also act on alpha 1 and H1 receptors [6, 7].

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This paper evaluates the efficacy, tolerability and safety of trazodone in its off-label uses.

METHODS

We conducted a review of the literature to identify and summarize the available knowledge regarding the clinical efficacy of trazodone, with special focus on its most common off-label uses to provide clinical guidance and direction for further research.

We analyzed the scientific material available on PubMed for the possible clinical uses of trazodone. The parameters of the search included articles published between 1970 and 2014, 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. There were no inclusion/exclusion criteria considered and no language restriction was placed on the literature search.

Articles examining the clinical uses of trazodone, including multiple psychiatric disorders and non-psychiatric disorders were included.

RESULTS

Insomnia

Insomnia, although widespread in the general population, is an underestimated and underdiagnosed condition. For instance, despite being one of the most frequent reasons of hardship in old age (over 65), sleep disorders are rarely diagnosed or treated, even by specialists in geriatrics [8, 9]. The continuity of sleep, rather than the difficulty in initiating sleep, is the most common problem among the elderly with sleep disorders [10, 11]. Despite a range of treatment options is available, there is still a paucity of pharmacological agents able to provide an optimal combination of therapeutic effects and tolerability. Few have been shown to improve sleep onset and

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continuity without any residual effects the next day and with no effects on cognitive functioning in the elderly [12].

Insomnia, whether primary or secondary, is the most frequent reason for prescription of trazodone [4-6, 13]. For this indication, trazodone is widely used as an alternative to benzodiazepines due to its hypnotic, anxiolytic and sedative actions and to the lack of an addiction risk [14].

Insomnia is a serious problem in this population, not only for its high prevalence, but also for the harmful consequences to the quality of life of those who suffer from it. For instance, sleep disorders in the elderly population are associated with significant increases in morbidity and mortality and with an increase in placement in nursing homes [15, 16].

The first evaluations of trazodone for the treatment of insomnia date back to two studies in the '80s [17, 18]. In the '90s the interest on the hypnotic effect of trazodone significantly increased and effectiveness in patients suffering from primary insomnia [19, 20] and those who suffer from insomnia associated with a depressive state began to be discussed more in depth [21-24].

More recently, the sedative effect of trazodone was compared with fluoxetine. A preliminary study reported the same effectiveness between the two drugs [25], while a second study in 1997 shows a slight advantage of trazodone compared to fluoxetine in relieving symptoms of insomnia in depressed patients [26].

Finally, two studies reported on a favorable sedative effect of trazodone in depressed patients treated with mono-aminoxidase inhibitors (IMAOs) [27].

In the past ten years, the efficacy of trazodone in the treatment of insomnia has been repeatedly demonstrated, both in its primary [28, 29] and secondary forms, as a symptom of depression [30-32] as well as when associated with dementia [33], or anxiety disorders like PTSD [34].

More recently, a double blind, four arm placebo-controlled randomized trial [35] compared low dose trazodone to Sentra PM, a neurotransmitter based medical food. The study included 111 subjects studied in 12 independent sites. The primary variables were sleep latency and parasympathetic autonomic nervous system. The results showed improvement in sleep latency and in sleeping hours induced by trazodone, while there was no change in parasympathetic activity.

In a recent trial, the effectiveness of trazodone has also been compared to quetiapine among psychiatric patients. Outcomes were evaluated by measuring the traditional sleep parameters of total sleep time, number of night-time awakenings, sleep efficiency, sleep latency, length of hospitalization, and patient-reported side effects, showing that, with respect to total sleep time and night-time awakenings, trazodone was found a more effective alternative than quetiapine [36]. Although the prevalence and standard treatment of nightmares in patients with cancer have not yet been established, a recent observational study suggested that trazodone may be an effective drug for the treatment of insomnia and nightmares in patients with advanced cancer [37]. Indeed, patients with cancer often experience insomnia and nightmares and more studies about this use are warranted.

A recent double-blind, randomized and controlled trial [38] showed significant therapeutic effects of trazodone 50 mg/day in community-dwelling patients suffering from Alzheimer Disease with sleep disorders.

Finally, in spite of trazodone's efficacy for sleep disturbances, this medication failed to show a significant improvement in subjective or objective sleep in methadone-maintained persons with sleep disturbance [39].

For many years trazodone has been proven to be a valuable tool for the treatment of insomnia. It should be stressed, however, that the data in the literature are limited, especially for primary insomnia. Most clinical trials have been short and objective measures of effectiveness in support of empirical observation are lacking [40].

In addition, further reservations about a widespread use of trazodone to treat insomnia result from the need to better evaluate side effects such as residual daytime sedation, dizziness, orthostatic hypotension, psychomotor impairment and priapism [15], as well as the possibility of establishing tolerance, especially after 1-2 weeks [40]. These factors raise doubts about the safe use of this drug in the elderly and may be the reason why in many Countries the use of trazodone in the treatment of insomnia remains off-label, and not yet officially approved by the FDA, despite the many encouraging clinical observations and relatively favorable results from the few large trials that have been conducted.

Other Sleep disorders. A few case reports have suggested the efficacy of trazodone for other sleep disorders. For instance, A 25-year-old man with narcolepsy and cataplexy experienced almost complete alleviation of the narcoleptic and cataplectic attacks within 48h after initiation of trazodone therapy, without the agitation and aggression side effects induced by methylphenidate [41]. Trazodone has also been found to increase the respiratory arousal threshold in patients with obstructive sleep apnea and a low arousal threshold without major impairment in dilator muscle activity or upper airway collapsibility. This effect was not sufficient to overcome the compromised upper airway anatomy in these patients [42].

Anxiety

Anxiety disorders have been shown to benefit from both pharmacological treatments and psychotherapies. The two primary classes of drug therapies are represented by benzodiazepines and antidepressants.

Benzodiazepines have anxiolytic and hypnotic properties and have been demonstrated to quickly control the clinical symptoms of many anxiety disorders. However, their efficacy in the long term may subside and some patients may end up using excessive doses.

Antidepressants remain a first line treatment for Generalized Anxiety Disorder whether or not associated with depression [43]. Trazodone has proven useful in the treatment of this disorder [44], with an efficacy comparable to that of imipramine and diazepam [45].

In Panic Disorder the utility of trazodone is not completely established yet. In some studies, trazodone failed to show favorable efficacy and tolerability [46], whereas other studies showed significant improvements in several clinical manifestations of panic disorder, as well as on generalized anxiety, phobias, depression and avoidance conduct, along with specific antipanic and antiphobic effect [47].

In Post-Traumatic Stress Disorder (PTSD), SSRIs are the treatment of first choice. Whenever SSRIs are not tolerated or are ineffective, medications such as trazodone may be a reasonable second-line treatment [48], with a significant improvement in social and occupational functioning [49]. Studies show very high percentages (70-91%) of sleep disturbances in association with PTSD, with special reference to difficulty in initiating and maintaining sleep [50] and trazodone may be a particularly favorable treatment for these symptoms [51]. In a study about the usefulness of trazodone in the treatment of insomnia and nightmares in patients with PTSD [34], 72% of the 60 participating subjects reported a decrease in nightmares, 92% found less difficulty in initiating sleep and 78% showed improvements in sleep maintenance.

In studies looking at Obsessive-Compulsive Disorder (OCD), with rare exceptions [52], there where no significant difference in efficacy between trazodone and placebo. Nevertheless, the literature is fairly unanimous in reflecting trazodone to be an useful drug in the treatment of this disorder [53], although with only mild improvements [54].

In one study, not only was trazodone shown to be clinical effective, but also had ability to reduce SSRI-induced side effects [55].

Other Off-Label Uses

Other, not officially approved, uses of trazodone include the treatment of: bulimia [56], benzodiazepines and alcohol dependence and abuse [57-59, 14], fibromyalgia [60], central nervous system degenerative diseases such as dementia and other organic disorders [61-63, 14], schizophrenia [64], chronic pain disease [14], diabetic neuropathy [65] and sexual dysfunctions [64] (Table **1**).

Bulimia

Antidepressants have long been used in the treatment of bulimia and no real difference in the efficacy and tolerability among the various classes has been shown [66]. Their effectiveness has been proven in bulimic patients who do not have concomitant depressive symptoms [67]. Trazodone, in particular, is well tolerated and effective in reducing the number of binge eating and vomiting episodes, compared to placebo [68, 69].

Benzodiazepines Abuse and Sleep Disturbances in Alcohol Withdrawal

Drug abuse and dependence are very common problems. Abstinence and the prevention of relapse are often the most desirable treatment goals. When possible, physicians should avoid drugs with potential for abuse or dependence [70]. Benzodiazepines represent a class of drugs with a broad spectrum of activity, rapid onset of action and a wide therapeutic range compared to other medications with anxiolytic action. However, their use is limited by the fact that they can induce dependence and abuse [71]. A 1993 study showed the usefulness of trazodone as an alternative to benzodiazepines in patients at risk of abuse [72].

As early as the '80s [57] and in the '90s [73], a possible off-label use of trazodone in the treatment of alcohol withdrawal syndrome has been suggested. In these cases the drug has shown to be useful in promoting abstinence and reducing the desire for alcohol. But since 2003, the research on this topic showed a growing interest. Sleep disorders are common among patients who are in alcohol withdrawal. Proper management of sleep is of paramount importance in these patients, especially in the early stages, since these sleep difficulties are considered triggers for many cases of relapse [58]. Trazodone is the most commonly used drug for this purpose, in view of the fact that it presents less risk of addiction and abuse than benzodiazepines [74]. In 2003, a study was conducted [75] through a postal survey of a sample of 503 members of the American Society of Addiction Medicine (ASAM) to assess the way these doctors managed sleep disorders in patients in early recovery from alcoholism. Of the physicians contacted, 62% answered the survey. The 64% of them prescribed their patients a pharmacological treatment. Despite the limited clinical evidence available, trazodone was found to be the most widely used among all the drugs. Beyond these purely empirical data, a study in 2008 [74] seems to emphasize the safety of trazodone therapy in patients who are at high risk of relapse. Although this study reaffirms the efficacy of trazodone in improving the quality of sleep in these patients during the initial treatment period, at the end of the therapy the quality of sleep matches that of placebo; then, the drug seems to undermine the progress in terms of days of abstinence during the period of treatment and to produce an increase in the number of drinks for drinking day at the end of the therapy. For these reasons, despite the little evidence in this regard, trazodone therapy cannot be recommended with sufficient certainty for the treatment of sleep disturbances during alcohol detoxification.

Currently, the role of pharmacological interventions in the initial stabilization of drug and alcohol dependent patients is not yet well established. Addiction is often a chronic and complex disorder associated with frequent relapses. Research is needed to identify medications that, on the short term, reduce or eliminate: the severe vegetative symptoms, pain, extremely distressing psycho-syndrome characterized by restlessness, anxiety or acute depressive symptoms and craving. The optimal would be if there was one medication capable of simultaneously alleviating or diminishing all the above symptoms without causing dependency and preventing relapse in the long-term. Early recovery from substance use dependency, in almost all cases, is accompanied by primary and/or secondary mood disorder or sleep disorder which should also be treated. Trazodone is effective in the treatment of depression accompanied by sleeping disorder and it has also shown efficacy in alcohol withdrawal and the treatment of benzodiazepine-dependency. Its administration may improve the efficacy of detoxification and treatment engagement, may decrease medication load and the risk of the development of benzodiazepine dependency, based on patients' reports and clinical observation of improvement of their depressive symptoms and sleep problems. Trazodone is a reasonable medication choice as it has been shown to decrease the risk of relapse and has low abuse potential [76]. However, more studies are needed before any specific recommendation, even as an off-label consideration, can be made.

Fibromyalgia

Trazodone has been shown effective in the treatment of fibromyalgia beyond its role of hypnotic agent. According to a recent study, not only did trazodone improve sleep quality in these patients, but also had a significant efficacy on other fibromyalgia symptoms, as measured by Fibromyalgia Impact Questionnaire, FIQ- [60]. It was also demonstrated that trazodone, in combination with pregabalin, significantly decreases the severity of fibromyalgia and its associated symptoms. Sleep quality, depression and the level of pain interference with daily activities were significantly improved [77].

Behavioural Disorders in Dementia

Since the '80s, a possible off-label use of trazodone in the treatment of behavioral disorders (irritability, anxiety, verbal aggression) associated with various forms of dementia has been suggested. However, the literature lacks consensus and fails to reach a conclusion. In the '80s and the '90s trazodone was considered by some to be useful despite the lack of confirmation in double-blind placebo-controlled studies [78], and its use is even recommended as an alternative to neuroleptics. In the late '90s this enthusiasm wained after a study comparing the efficacy and side effects of trazodone compared to haloperidol, showing that there was no significant difference in terms of effectiveness. Differences were noted with regard to side effects, most common in the group of patients treated with haloperidol [79]. In the last decade, with some exceptions [80], the authors were more cautious on this subject, in some cases promoting the effectiveness of trazodone limited to some of the Behavioral and Psychological Symptoms of Dementia (BPSD) associated with the Alzheimer Disease -such as aggression and negativism in caregiving situations-. In another study, patients treated with trazodone did not show any improvement in BPSD after 6 months of treatment [63]; in yet another, the clinical efficacy of the drug was totally questioned, since the comparison with placebo did not show significant benefits [81]. More recently, the use of trazodone as an excellent therapeutic option in elderly patients with dementia associated with sleep disorders has been demonstrated [35], confirming that the drug's greatest qualities may be in its use as hypnotics.

Currently, there are relatively few studies of antidepressants for the treatment of agitation and psychosis in dementia. The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo. Both SSRIs and trazodone appear to be safe and effective treatments for agitation and

psychosis in dementia compared to placebo, typical antipsychotics and atypical antipsychotics [82].

Due to their increasing frequency, mental disorders among the elderly have special importance in clinical practice. This period of life is often associated with specific somatic and psychic problems that negatively impact in the elderly's function. It is often difficult to find the most effective and well-tolerated treatment, especially in case of comorbid dementia or agitated behavior. Due to its special anxiolytic and sleep normalizing effect, as well as its well-tolerated side effect profile, trazodone has been found to be clinically useful in the treatment of depression in the elderly, but also in cases of serious comorbidity of dementia or agitated behavior [83].

Schizophrenia

Serotoninergic antidepressants, used in combination with neuroleptics, are safe and effective in the treatment of negative symptoms in elderly patients with chronic schizophrenia [84]. Trazodone has been shown to significantly reduce the severity of negative symptoms without increasing the positive ones, but the magnitude of the therapeutic effect remains modest [85]. According to a recent study, trazodone has been proven to be effective in the treatment of neuroleptic-induced acute akathisia, an extrapyramidal symptoms often arising from the use of antipsychotics. Despite the high incidence of this disorder, its mechanism of action has not yet been adequately explained. However, it would appear that the clinical efficacy of trazodone, in this case, is to be attached to its property of postsynaptic 5-HT2A receptor antagonist [86].

Acute Neuroleptic-Induced Akathisia

Akathisia is a distressful and relatively common extrapyramidal side effect, usually resulting from the use of antipsychotic medications. Akathisia pathophysiology has not yet been adequately explained. In addition to dopaminergic mechanisms, it has been hypothesized that serotonin may play a prominent role, but a specific evidence is still lacking. Owing to its postsynaptic 5-HT2A receptor antagonist, trazodone may be safe and effective in the treatment of neuroleptic-induced akathisia [87, 88]. This would be consistent with similar observations, showing that mirtazapine may 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. Hence, mirtazapine would have a dose-related bi-directional effect on akathisia, with low doses exerting an anti-akathisia effect and higher doses inducing akathisia [89]. Similarly, the antidepressant mianserine, that shares with trazodone a marked 5-HT2A antagonism at low doses, showed anti-akathisia characteristics in antipsychotic-treated schizophrenic patients [86]. Nefazodone, presently withdrawn from the market because of severe epatotoxicity, was a medication with a possible therapeutic role in the treatment of antipsychotic-induced akathisia, owing to the blockage of postsynaptic 5HT2A receptors [90]. Trazodone, mirtazapine, mianserin and nefazodone share, indeed, serotonergic antagonistic properties, and these activity may be key in the treatment of neuroleptic-induced acute akathisia.

Chronic Pain Disorders

Patients presenting with chronic pain are a challenging problem nearly all physicians encounter in their practice. According to some theories, although rather dated [91], serotonin was thought somehow to be involved in the mechanism that leads to the development of chronic pain. This hypotheses led some to think that drugs, including trazodone, which inhibit the reuptake of serotonin, may be useful in the treatment of various pain syndromes. In a study of patients with dysesthetic pain syndrome (DPS) [92], comparing trazodone to placebo no difference was noted; in addition to no difference in the benefit experienced, a significant number of patients assigned to active drug group complained of side effects which led them to prematurely leave the study. Even in the case of chronic low back pain syndrome [73] there were no significant differences between the group assigned to trazodone and the patients assigned to placebo. The same is true in the case of burning mouth pain [93], where the trazodone completely disappointed the expectations. The only case in which trazodone showed a real efficacy towards a pain syndrome, is a study in 1999 [65], in which trazodone was proven to be useful in the treatment of pain associated with diabetic neuropathy.

Sexual Disorders

The unusual side effect of trazodone, priapism, led researchers to evaluate the use of this drug in the treatment of erectile dysfunction. The literature is controversial on this topic. Some studies seem to disappoint the expectations, asserting that trazodone is no more effective than placebo in improving erections and sexual function [94-96]. However, other studies indicate trazodone can be used as adjuvant therapy in the treatment of male non-organic sexual dysfunction [97], although the improvement is not statistically significant [98]. According to a more recent study, trazodone was shown to be effective, safe, fast acting and with few side effects in treating sexual dysfunctions [99]. There are also those who demonstrated its effectiveness in the management of SSRI-induced sexual dysfunctions, a problem which is often a cause of therapy discontinuation or of a reduced compliance by the patient, resulting in failure of the treatment itself [64], despite the fact that trazodone has not officially approved for patients with urological conditions. There remains a lack of understanding of the complete mechanism underlying SSRI-induced sexual dysfunction. By raising serotonin at all serotonin receptors, SERT inhibitors, such as SSRIs, simultaneously cause antidepressant actions by stimulating 5-HT1A receptors, but create adverse effects by stimulating 5-HT2A and 5-HT2C. However, when SERT inhibition is combined with 5-HT2A and 5-HT2C inhibition, this leads to an antidepressant action without sexual disorders. It is suggested that drug antagonism on serotonin receptors, such as trazodone, may improve sexual function reverting the stimulation of serotonin receptors by SSRIs, acting as 5-HT2 antagonist [64]. These effects could be due to its action on α-adrenoceptor antagonists in the periphery [7, 99] and to a central mechanism, still unknown [100].

Association with SSRIs

Because of its 5HT2A receptor antagonistic action, trazodone has been shown to prevent the occurrence of initial and long-term side effects of SSRIs, in particular anxiety, insomnia and sexual dysfunctions [6, 64]. However, there is a theoretical rationale which suggests the possibility of a synergistic antidepressant action, as well as an increased tolerability, in case of association between trazodone and SSRIs drugs [101, 102].

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 5HT2A receptor and inhibited at the level of 5HT1A receptor; consequently, a balance between these two mechanisms results in no net effect (excitation or inhibition). Theorically, 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 5HT1A receptor. However, when serotonin levels increase, due to the block of SERT mediated by the SSRIs, both 5HT1A and 5HT2A receptors are simultaneously stimulated, with no net effect on the neuron; when trazodone blocks 5HT2A receptors while 5HT1A receptors continue to be stimulated, both the inhibitory effect against the neuron and the consequent antidepressant effect are potentiated [101, 103]. Another mechanism that could explain the synergistic effect between the antagonism 5HT2A and the SERT block can be found in an increased release of dopamine and norepinephrine in the prefrontal cortex [104-108]. The

stimulation of serotonin 5HT2A receptors inhibits the release of these neurotransmitters through a GABAergic mechanism; trazodone, blocking 5HT2A receptors, would be able to uninhibite this release, thereby enhancing the antidepressant effect of SSRIs. As regards a possible association between trazodone and fluoxetine, the latter has no significant impact on trazodone serum levels, so we assume that there is no metabolic interaction between these drugs. We can observe none of the side effects which may have been expected (dizziness, severe headache, daytime sedation, fatigue, serotonin syndrome even in a mild form) [109]. However, fluoxetine-induced increase in plasma mCPP concentrations can be observed and it 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 [110].

Although many pharmacological characteristics of trazodone suggest a clear potential synergistic action towards SSRIs, it remains a pure theoretical consideration. No clinical study so far has shown that the addition of a 5HT2A antagonist to SSRIs is able to enhance their antidepressant effect. However, it is undeniable that this notion is perfectly consistent with the observations that atypical antipsychotics, which have antagonistic effects on 5HT2A receptors for serotonin as a property of the first level, are able to enhance the response to SSRIs in some depressed patients, especially those with resistant depression [6, 7]. Despite the interesting hypotheses derived from pharmacodynamic, at present there are no studies in the literature to support such empirical data.

Trazodone Side Effects

Among the adverse effects of trazodone, there are daytime sleepiness and excessive sedation [111-116], headache, dizziness and hypotension. There have been reports of priapism (as in the case of other adrenolytic drugs) with increased libido and extension of nocturnal erections reported in clinical practice -for this reason trazodone is considered effective in the treatment of sexual dysfunctions- [97, 99, 117-119]. Patients who are at high risk for the development of priapism include patients with sickle cell anemia or sickle trait, leukemia, autonomic nervous system dysfunctions or hypercoagulable states. In addition, high risk patients include those who are taking SSRIs (dose-related) and those who used cocaine or 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 [120]. The occurrence of gastric distress, nausea, vomiting and decreased appetite has been rarely reported [121]. It should not be underestimated the potential arrythmogenic risk due to the adrenergic receptors block -prolonged QTc- [122]. 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 [123]. 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 [113], 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 [124]. In a case study, after a single dose of trazodone, a patient developed complete heart block [125]. Despite the results of earlier studies, trazodone's effect on cardiac conduction may be severe in individuals at risk for conduction delay.

Trazodone-induced delirium was observed in depressed patients who also suffered from preexisting organic cerebral lesions and/or thyroideal dysfunction. The appearance of hallucinations, psychomotoric agitation, and cognitive changes after initiation of tra-

Table 1. Off-label uses of Trazodone, results.

Off-label uses of Trazodone	Results
Insomnia	Encouraging clinical observations, favorable results.
Anxiety	Improvements in avoidance conduct of Panic Disorder, specific antipanic and antiphobic effect in Generalized Anxiety. Decrease in nightmares and sleep disorders in Post-Traumatic Stress Disorder. Mild improvements in Obsessive-Compulsive Disorder.
Sexual disorders	SERT inhibition combined with 5-HT2A and 5-HT2C inhibition leads to an antidepressant action without sexual disorders. Action on α-adrenoceptor antagonists in the periphery.
Substance abuse	May improve the efficacy of detoxification, decrease medication load and the risk for benzodiazepine and alcohol dependency. Low abuse potential.
Bulimia	Well tolerated and effective in reducing the number of binge eating and vomiting episodes.
Fybromialgia	Improvements in sleep quality, depression and the level of pain interference with daily activities.
Dementia	Clinically useful in the treatment of depression in the elderly, but also in cases of serious comorbidity of dementia or agitated behavior.
Schizofrenia	Modest efficacy on the negative symptoms of schizophrenia; effective in the treatment of neuroleptic-induced acute akathisia, due to its property of postsynaptic 5-HT2A receptor antagonist.
Chronic pain	Useful in the treatment of pain associated with diabetic neuropathy.
Combination with SSRIs	Synergistic antidepressant action (augmentation, acceleration effect), as well as increased tolerability.

Table 2. Trazodone adverse effects.

Trazodone Side Effects	
Sedation	Prefer evening administration.
Postural Hypotension	Less likely to appear if the drug is taken with meals.
Priapism	High risk for patients with sickle cell anemia or sickle trait, leukemia, autonomic nervous system dysfunctions or hypercoagulable states. These cases should be treated cautiously and alternative therapeutic strategies should be considered.
Gastric distress, nausea, vomiting	Rarely reported.
Cardiac Arrhythmias	Due to the adrenergic receptors block -prolonged QTc- and/or cardiac HERG potassium channels blockade.
Delirium, hallucinations, psychomotoric agitation, cognitive changes	Drug-induced phenomena in preexisting organic cerebral lesions and/or thyroideal dysfunction. Due to oversensitivity to the effect of meta-chlorphenylpiperazine, trazodone metabolite with specific 5-HT agonistic properties.
Serotonin Syndrome	It can be rarely observed during treatment with trazodone, almost in association with other serotomimetic agents (SSRIs, tricyclic antidepressants, MAOIs).

zodone therapy and their prompt cessation after drug discontinuation led to the impression that these were drug-induced phenomena. One possible hypothesis for the observed deliria is an oversensitivity to the effect of meta-chlorphenylpiperazine, which is a metabolite of trazodone with specific 5-HT agonistic properties [126]. Shiotsuki [127] also suggests that trazodone may induce auditory hallucinations in some susceptible patients. Although trazodone 100 mg was found to cause cognitive driving impairment [128], a more recent study demonstrated that it does not affect driving performance or cognitive function under acute or repeated administrations, despite its sedative effect [129].

The Serotonin Syndrome is characterized by various combinations of myoclonus, rigidity, hyperreflexia, shivering, confusion, agitation, restlessness, coma, autonomic instability, low-grade fever, nausea, diarrhea, diaphoresis, flushing, and rarely, rhabdomyolysis and death, which can occur following the use of serotomimetic agents. It can be rarely observed during treatment with trazodone, almost in association with other drugs such as SSRIs, tricyclic antidepressants, MAOIs [130], suggesting that the combination with these molecules facilitates the effect of central serotonergic responses mediated by trazodone (Table **2**).

CONCLUSION

Trazodone is a well-tolerated and effective medication for insomnia. Trazodone may also be of help in reducing the number of binge eating and vomiting episodes in bulimia and has been found to significantly improve some of the symptoms associated with fibromyalgia. Moreover, trazodone may be of help for patients suffering from anxiety symptoms and at risk of benzodiazepine abuse. Studies on the off-label use of trazodone in the treatment of behavioral disorders associated with dementia have not always led to clear cut conclusions. However, trazodone has recently been judged as a valuable therapeutic option in patients with dementia associated with sleep disorders. Trazodone evidences for efficacy on the negative symptoms of schizophrenia remain modest, but this medication may be useful in the treatment of acute neuroleptic-induced akathisia, possibly because of its postsynaptic 5-HT2A receptor antagonism. Trazodone may also help with the treatment of pain associated with diabetic neuropathy as well as in the management of SSRI-induced sexual dysfunction.

Despite the many and mostly favorable preliminary results, the need to improve research on trazodone is clear. To date, randomized placebo-controlled trials represent an even smaller minority. This does not help to ensure adequate scientific evidence to justify the use of the drug in a large variety of diseases. Although off-label use should not be encouraged, the wide range of off-label applications in clinical practice clearly warrants further research.

CONFLICTS OF INTEREST

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