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CLINICAL FEATURE
REVIEW

A review of trazodone use in psychiatric and medical conditions

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ABSTRACT

Trazodone is an antidepressant that is FDA-approved for the treatment of depression. It has been used by mental health and primary care providers for the treatment of multiple psychiatric and medical conditions .This review describes trazodone mechanism of action, formulation, dosage and adverse effects and then summarizes the beneficial effects of trazodone in the treatment of various psychiatric and medical conditions such as major depression, as well non-approved FDA indications such as insomnia,anxiety disorders, posttraumatic stress disorder, obsessive compulsive disorder, feeding and eating disorders, substance use disorders, behavioral disturbances associated with cognitive dysfunction, sexual dysfunction, certain pain conditions, and rehabilitation after acute ischemic stroke. Despite trazodone's favorable effects in the treatment of FDA-unapproved psychiatric and medical conditions, large, randomized controlled clinical trials are still needed to confirm its efficacy in the treatment of the multiple conditions for which it is often used in clinical practice.

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1. Introduction

Trazodone was introduced in Europe and Asia in the early 1970s and was approved for use in the US in 1978. Since then it has been approved and marketed in several countries worldwide for the treatment of major depressive disorder (MDD) in adult patients. Trazodone belongs to the class of serotonin receptor antagonists and reuptake inhibitors (SARIs) [1]. Several randomized controlled studies have demonstrated trazodone antidepressant activity when compared with tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and the serotonin–nor adrenaline (nor epinephrine) reuptake inhibitors (SNRIs). Beyond its antidepressant activity, trazodone was found to be beneficial in the treatment of medical and psychiatric conditions including insomnia, anxiety disorders, posttraumatic stress disorder, obsessive compulsive disorder, feeding and eating disorders, substance use disorders, behavioral disturbances associated with cognitive dysfunction, sexual dysfunction, certain pain conditions, and rehabilitation after acute ischemic stroke [2,3]. Recently, there has also been a renewed interest in reconsidering trazodone as an effective antidepressant especially with the release of its delayed-release formulation [4].

2. Mechanism of action

Trazodone is an antidepressant that is structurally different from the SSRIs, TCAs, and the monoamine oxidase inhibitors (MAOIs). It is characterized by lower anticholinergic properties and lower cardiac conduction effects than the TCAs [1].

3. Trazodone pharmacodynamics

Trazodone is a phenylpiperazine and a triazolopyridine derivative that acts as an antagonist of serotonin type 2 receptors (5-HT2) and α-adrenoreceptors, as well as an inhibitor of 5-HT reuptake which play a role in its antidepressant and anxiolytic effects [5]. Along with nefazodone and vilazodone, trazodone belongs to the class of the serotonin receptor 5-HT2 antagonists and 5-HT reuptake inhibitors (SARIs) [6,7].

4. Trazodone pharmacokinetics

Trazodone is well absorbed after oral administration without selective localization in any tissue. When it is taken shortly after ingestion of food, there may be an increase in the amount of its absorption, a decrease in maximum concentration and a lengthening in the time to maximum concentration. Peak plasma levels occur approximately 1 h after dosing when trazodone is taken on an empty stomach or 2 h after dosing when taken with food [8,9]. Trazodone is highly (89% to 95%) protein-bound and is extensively metabolized, by CYP3A4. Less than 1% of an oral dose is excreted unchanged in the urine and around 70–75% of 14 C-labeled trazodone was found to be excreted in the urine within 72 h [10].

Although several metabolic pathways involved in the metabolism of trazodone are not well characterized; meta-chlorophenylpiperazine (mCPP) is considered one of its most active metabolite [11]. Trazodone metabolism is enhanced by smoking, and not affected by age, gender or the coadministration

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of benzodiazepines which suggest the presence of linear kinetics between trazodone and mCPP [12]. Additionally mCPP has been shown to activate numerous serotonin receptors, including 5-HT2C, which could be used as a challenge agent to assess 5-HT receptor sensitivity. When mCPP is given at a low oral dose (i.e. around 0.25 mg/kg), it would assess 5-HT receptor hypersensitivity; while if mCPP is given at a high oral dose (i.e. around 0.5 mg/kg) would assess 5-HT receptor hyposensitivity [13]. As a 5-HT reuptake transporter (SERT) and 5-HT2C agonist mCPP could possibly contribute to trazodone antidepressant and anxiolytic effects. Genetic studies of the cytochrome P450 CYP2D6 genotype suggest that this genotype cannot predict the steady-state plasma concentrations (Css) of trazodone and its active metabolite mCPP [14].

Since the metabolism of trazodone into mCPP involves the isoform CYP3A4, this could potentiate drug–drug interactions with other substrates, inducers and/or inhibitors of the same cytochrome P450 (P450)2 enzymes. Clinicians prescribing other medications that are metabolized through the CYP3A4 and the cytochrome P450 (P450)2 enzymes system need to be aware of these interactions which could lead to a decrease or a loss of trazodone therapeutic effects, or could cause new side effects and in rare but severe cases could lead to death.

For instance CYP3A-mediated clearance of trazodone is inhibited by ketoconazole, ritonavir and indinavir, and should be taken in consideration when patients are receiving these agents for the treatment of HIV while coadministered trazodone [15]. Because CYP2D6 is also involved in the metabolism of trazodone and is the isoform responsible for the hydroxylation of mCPP, caution should be exercised in coadministering inhibitors or substrates of CYP2D6 with other medications that have mCPP as a metabolite such as thirodazine [16,17]. Trazodone is sedating in all age groups, its prolonged sedative effects in the elderly may not be related to the effects of trazodone on the elderly but probably due to an age-related reduction in its hepatic metabolizing activity, a difference in regional distribution or a change in central nervous system (CNS) sensitivity to trazodone [18]. The reduced clearance of trazodone in the elderly may require dosage reduction during long-term therapy [18,19]. In individuals with increased body weight the choice of trazodone dose during long-term treatment should be based on the ideal body weight rather than the total body weight [19].

5. Administration and dosage

Trazodone is available in two formulations the immediate release (IR) and the extended release(ER).

- IR: This formulation [2] is typically started at 50 mg twice daily, which is then increased by increments of 50 mg per day every 3–7 days to a dose of 75–150 mg twice daily. The dose is subsequently increased by 50–100 mg per day every 2–4 weeks until the desired clinical response is achieved, to a maximum dose of 600 mg per day. Doses >400 mg per day warrant cautious use and additional monitoring, particularly in the elderly and other patients at risk for cardiovascular toxicity. The sedative effects may be better tolerated if patients are given a smaller daytime dose and larger bedtime dose (100 mg in the morning and 200 mg at bedtime) however some patients take the entire dose at bedtime without adverse effects.
- ER: The ER formulation allows a once-daily convenient dosing thus facilitating patient adherence and consequently leading to an improvement in MDD treatment [8]. It was approved by the Food and Drug Administration (FDA) in February 2010. It was designed to eliminate the peaks and troughs in serum concentration associated with the IR formula. It is hypothesized that by reducing the maximum concentration (Cmax) peaks, trazodone ER would permit higher doses to be better tolerated and would help patients reach target antidepressant doses. The ER tablets are dose proportional following single-dose administration of doses ranging from 75 to 375 mg as intact or bisected tablets. It provides both a rapid and a sustained release that maintains blood levels within the therapeutic range for 24 h, thus potentially reducing the incidence and severity of adverse events while maintaining antidepressant efficacy. Trazodone ER has a linear pharmacokinetics in doses from 75 to 375 mg. The 300 mg daily doses, provide a steady-state exposure equivalent to 100 mg of trazodone IR given three times daily, and reduce the maximum concentration (Cmax). It is usually started at 150 mg at bedtime. For patients who do not respond after 2–4 weeks, the dose is increased to 225 mg at bedtime. The dose is subsequently increased by 75 mg per day every 2–4 weeks until the desired clinical response is achieved, to a maximum dose of 375 mg per day. In clinically urgent inpatient treatment, dose increases can occur every 3 days as tolerated.

6. Adverse effects

Trazodone gastrointestinal side effects may include nausea, vomiting, diarrhea, or constipation. Cardiovascular side effects may include orthostatic hypotension, particularly in the geriatric population and in patients with underlying heart disease, arrhythmias, corrected QT interval prolongation and torsade de pointes could also occur [2]. Other general side effects include drowsiness, dizziness, tiredness, blurred vision, changes in weight, headache, muscle ache, dry mouth, and a rare side effect of seeing visual trails of images following eye movements [4]. Side effects usually subside with the passage of time and in certain cases with dose reduction.

The association of priapism with trazodone has been reported to the FDA based on collected data [20] which suggest that priapism may be most likely to occur within the first 28 days of treatment and that the majority of cases occur with doses of 150 mg/day or less. All age groups appear to be vulnerable to this adverse effect. Patients should be informed of this potential side effect and instructed to discontinue the medication if any unusual erectile problems develop [20]. Other risk factors for developing priapism include the combination of trazodone with SSRIs, cocaine or atypical antipsychotic medication [21]. Priapism need to be promptly and

surgically treated to prevent permanent impotence due to the damage of the penis vascular structures [22].

Patients who experience high degree of sedation or significant drowsiness should not drive or operate hazardous machinery immediately after taking trazodone. Rapid or abrupt discontinuation of trazodone may be followed by undesirable side effects, which are sometime referred to as withdrawal symptoms, including gastrointestinal distress, anxiety, and sleep disturbances [23]. Thus, tapering it over 2–4 weeks prior to discontinuation is clinically indicated.

Trazodone appears to be relatively safer than TCAs, MAOIs, and a few of the other second-generation antidepressants in intentional or accidental overdose events, especially when it is the only agent taken and when it is not combined with alcohol and or other sedative or hypnotic agents . Fatalities are rare, and uneventful recoveries have been reported after ingestion of doses as high as 6000–9200 mg [24]. When trazodone overdoses occur, careful monitoring should be initiated to assess hypotension, the emergence of torsades de pointes and for the possibility of complete atrioventricular block, along with subsequent multiple organ failure, which could occur with a trazodone plasma concentration of 25.4 g/mL [25,26].

7. Pregnancy and lactation

The effects of trazodone on the developing fetus in pregnant women are not fully known and it does not seem to increase the rates of major malformations above the baseline rate of 1–3% [27]. To minimize the risk of recurrence of depressive symptoms, trazodone could be restarted or an alternative antidepressant with known safety during pregnancy could be initiated [27,28]. Trazodone is excreted in breast milk and nursing mothers should be advised to discontinue trazodone, due to its unknown effects on babies [28]. If stopping the medication is not an alternative, breast-feeding should not be started or should be discontinued.

8. Drug–drug interactions

Trazodone can potentiate the effects of other CNS depressants including alcohol. Patients should be educated about the risk of increased drowsiness and sedation which could affect alertness level and thus affecting driving and the ability to operate machinery and heavy equipment [29]. Trazodone is a relatively potent α-2 antagonist, so subsequently it could block the antihypertensive effects of the α-2 agonist clonidine [30] thus requiring frequent monitoring of blood pressure in patients receiving both medications. Because of trazodone's possible orthostatic hypotensive effects, the concomitant administration of trazodone with antihypertensive agents may require a reduction in the dose of the antihypertensive agent.

There is also a potential for a trazodone and warfarin interactions in patients receiving anticoagulant treatment leading to a decreased prothrombin time (PT) and decreased international normalized ratio (INR) [31].

Patients receiving MAOs or intravenous methylene blue should have at least 14 days washout period before receiving trazodone to prevent the possibility of developing serotonin syndrome which is considered a medical emergency manifested by tachycardia, severe drooling, restlessness, diaphoresis, whole-body tremor, inducible foot clonus, predominant lower limbs rigidity, bilateral pupil dilation, increased bowel sounds with watery diarrhea, and muscle hypertonicity [32]. Due to linezolid MAOI activity the combined administration of this antibiotic with trazodone has also been associated with emergence of serotonin syndrome [33].

Mania has been observed in association with trazodone treatment which could occur in patients with bipolar disorder as well as in patients with previous diagnoses of unipolar depression [34]. Due to this potential adverse effect, clinicians should avoid prescribing trazodone for the management of insomnia or depression in patients with bipolar disorder unless these patients are adequately treated and maintained on mood stabilizers.

In general trazodone is not recommended for use below the age of 18 years. Nonetheless, when the potential benefits of reducing severe symptoms of depression outweigh the potential risks for side effects, it may be prescribed 'off label' in children and adolescents, especially in those with insomnia and MDD [35].

Because the incidences of both anticholinergic and cardiovascular effects are lower with trazodone compared with the TCAs, it was especially welcomed as a treatment for geriatric patients with depression when it first became available [4,36]. It can also be of use in elderly patients in whom anxiety and insomnia are problematic, and in those patients who are unresponsive to or cannot tolerate therapy with other antidepressants [4].

Although therapeutic blood levels of trazodone have not been established, its dosing needs to be adjusted based on patients' age. The average doses of trazodone in various patients' population are summarized in Table 1.

Table 1. Trazodone dosages in various population.

Adult	Pediatrics	Geriatrics
Immediate release Initial 150 mg/day orally divided every 8–12 h Increase by 50 mg/day every 3–7 days Outpatient: No more than 400 mg/day Inpatient: No more than 600 mg/day **Extended release** 150 mg orally initially at bedtime; may increase by increments of 75 mg/day every 3 days; not to exceed 375 mg/day Swallow whole or may break in half along scored line; do not chew or crush	**Immediate release** <6 years: safety and efficacy not established 6–12 years: 1.5–2 mg/kg/day orally in divided doses initially; not to exceed 6 mg/kg/day divided every 8 h >12 years: 25–50 mg/day po; increase by 100–150 mg in divided doses	**Immediate release** 25–50 mg orally at bedtime; increase dose by 25–50 mg every 3 days if inpatient or every week if outpatient not to exceed 75–150 mg/day **Extended release** 150 mg orally initially at bedtime; may increase by increments of 75 mg/day every 3 days; not to exceed 375 mg/day Swallow whole or may break in half along scored line; do not chew or crush

9. Trazodone black box warnings

In the course of short-term clinical studies some children, teenagers, and young adults (up to 24 years of age) receiving trazodone for treatment of MDD developed suicidal tendencies including thoughts and plans to kill themselves. However, experts are not sure about the degree and severity of this risk, and although it should be considered in deciding the usefulness of using trazodone, it should not prevent its use, since there are greater risks for suicide in untreated MDD.

Education should be provided to families and significant other to report any abrupt changes in behavior to the healthcare providers. The development of suicidal tendencies that are not a component of the presenting symptoms of depression may require discontinuation of trazodone therapy.

10. Summary of trazodone use in medical and psychiatric conditions

10.1. Major depressive disorder

Major depressive disorder (MDD) is considered the second leading cause of disability worldwide and a major contributor to the burden of suicide [37]. Trazodone is an FDA approved antidepressant which is as effective as other classes of antidepressant medications such as TCAs, SSRIs and SNRIs [38]. It can be used as monotherapy or as an augmenting agent in combination with other antidepressant medications for the treatment of resistant MDD [39]. Trazodone is effective in controlling a wide range of symptoms of depression such as decreased interest in pleasurable activities, feeling of sadness and hopelessness, disturbed appetite, low energy level and suicidal thoughts, while avoiding the sleep difficulties that have been associated with the use of some SSRIs [3]. Trazodone can also be used off-label as an adjunctive agent to counteract the adverse effects and decreased tolerability that are often associated with the SSRIs especially insomnia, anxiety and sexual dysfunction [2,4]. The prolonged-release formulation could provide further optimization of trazodone antidepressant effects and may be useful in enabling an appropriate therapeutic dose to be administered in addition to improving patient compliance [8]. Despite the possible side effects of orthostatic hypotension especially in the elderly, trazodone has similar efficacy and better tolerability than TCAs for treating MDD in the geriatric populations [40,41].

10.2. Insomnia

It has been estimated that 50–70 million adults in the U.S. have chronic sleep and wakefulness disorders .The National Health and Nutrition Examination Survey (2005–2010), showed that approximately 4% of U.S. adults 20 years of age and older have used medications to address their sleep difficulties and insomnia [42]. Trazodone has been frequently used for the treatment of primary or secondary insomnia with or without depression [43,44]. Decades of clinical experience suggest that low-dose trazodone is effective for sleep in a variety of contexts, particularly in the setting of psychiatric illness and its use could benefit many patients who develop side effects and addiction to many available sedative and hypnotic agents [43–48]. However it is important to note that the use of trazodone's efficacy in treating insomnia has been mostly derived from small studies, conducted in populations of depressed patients, associated with design issues, and often with lack of objective efficacy measures [49]. Clinicians prescribing trazodone for treatment of insomnia and sleep difficulties need to be aware of its side effects especially sedation and dizziness, which contribute to its discontinuation. Additionally patients who develop tolerance to trazodone hypnotic effects would require alternative medications to treat their sleep difficulties.

10.3. Anxiety disorders

Due to its anxiolytic properties trazodone has been used for the treatment of anxiety disorders with or without depression. Trazodone has been beneficial in the treatment of generalized anxiety disorder (GAD) and panic disorder (PD) [50].

- Patients with GAD experience disabling symptoms of excessive physiologic arousal, distorted cognitive processes and poor coping strategies. Although GAD is usually treated with benzodiazepines, SSRIs or SNRIs [51], a substantial number of patients do not respond well to these classes of medications and some develop troublesome side effects, for these patients trazodone could be used as an alternative and a well-tolerated treatment [51].
- Patient with PD usually experience periods of intense fear or discomfort associated with many somatic symptoms such as chest pain, dizziness, nausea, chills, trembling, and palpitations that could escalate to a full blown panic attack prompting emergency intervention due to an unrealistic fear of imminent death. Some patients with panic attacks also develop increased worries about having future attacks which could lead in an alteration in consequent behaviors whereby they become totally afraid of leaving their home and develop agoraphobia. Trazodone has been shown to improve PD and agoraphobia in patients who did not respond to other pharmacological interventions [52]. In other cases, trazodone was reported to be ineffective and poorly tolerated in patients with PD [53].

10.4. Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) is a psychiatric condition, that develop following exposure, witnessing or experiencing life threatening traumatic events. It is usually manifested by four main PTSD symptom clusters which include intrusion with nightmare or unwanted thoughts about the traumatic events, avoidance of reminders that could trigger traumatic memories, negative alterations in cognitions and mood and disturbed arousal and reactivity such as increased startle response, and hypervigilance [54]. Although the first-line treatment option for PTSD is the SSRIs, trazodone may be used if SSRIs are ineffective or intolerable [55]. Some patients with combat-related PTSD, responded to trazodone treatment and reported a decrease in

nightmares and an improvement in an overall sleep quality [56]. Trazodone can also be used to augment the antidepressant and anxiolytic effects of the various SSRIs that are used in the treatment of patients with PTSD [57].

10.5. Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is an intriguing, yet difficult condition characterized by intrusive unwanted thoughts and performance of certain rituals to counteract these thoughts. This condition usually respond to SSRIs treatment and some patients with OCD showed symptomatic improvement following the addition of trazodone to various SSRIs, and in some cases, trazodone also improved the SSRIs tolerability [4,58].

10.6. Feeding and eating disorders

Trazodone was found to be beneficial in the treatment of bulimia nervosa and nighttime eating disorder [59–64]

- Bulimia nervosa (BN), is a feeding and eating disorder which is characterized by frequent episodes of binge eating followed by inappropriate behaviors such as self-induced vomiting, misuse of laxatives, diuretics, or other medications in addition to fasting, or excessive exercise to avoid weight gain [59]. Although the SSRI fluoxetine is the only antidepressant that is FDA approved for the treatment of BN, trazodone was found to be effective in decreasing frequency of binge eating and vomiting and in producing fewer adverse effects especially in the context of not gaining weight [4]. The lack of weight gain represented an advantage in these patients who are constantly fearful about gaining weight.
- Night eating syndrome (NES) is an eating disorder, which is included in the 'Other Specified Feeding or Eating Disorder' category of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [60]. It is characterized by a delayed circadian pattern of food intake where 25% or more of the total daily calories is consumed after the evening meal and/or during nocturnal awakening [61]. Patients with NES are totally aware of their night eating patterns [62] which differentiate them from patients with other sleep-related eating disorders (SRED). As in the case of other eating disorders, morning anorexia and restrictive eating at lunch are also common in NES [63]. Although most patients with NES have a depressed mood, they may not be suffering from MDD [64]. Some patients with NES are euthymic in the morning, then their mood gradually worsen and reach a degree of marked distress, resulting in evening and night overeating episodes [65]. Trazodone may benefit certain patient with NES [62].

10.7. Substance use disorder

10.7.1. Alcohol use disorder

Trazodone offers an advantage in treating insomnia during alcohol withdrawal in contrast to other hypnotics such as the benzodiazepines due to their risk of drug to drug interaction and cross tolerance with alcohol [4,66,67]. Although some clinicians are concerned about treating insomnia with trazodone in patients with alcohol use disorder because it might adversely lead to increased drinking when trazodone is stopped [68]. Conducted research did not find an association between trazodone use and increased alcohol relapse rates [69].

Despite these preliminary findings more controlled clinical trials with trazodone as an adjuvant medication for alcohol withdrawal treatment are still needed.

10.7.2. Cocaine use disorder

Cocaine addiction remains a high-morbidity, chronic relapsing illness with several complications and fewer treatment options [70]. The feelings of tension and shakiness that is induced by cocaine administration could diminish with the use of trazodone [71]. One of the complications of cocaine use is the developing of a foraging which is a compulsive behavior of searching for pieces of crack cocaine that the individual believes might have been accidentally misplaced. The use of trazodone led to remission of cocaine-induced compulsive foraging behavior and resulted in the prevention of relapse into cocaine use in three patients with long history of abusing crack cocaine [72].

10.8. Behavioral disturbances associated with cognitive dysfunction

Behavioral disturbances in patients with cognitive dysfunction could be a considerable precipitating factor for violence toward self and others, and contribute to family distress and burden for caregivers. The behaviors of the cognitively impaired could severely disrupt personal, social, institutional relationships and frequently lead to acute hospitalization, long-term institutional placement and may lead to caregiver 'burnout'. Behavioral disturbances in patients with dementia are amenable to pharmacotherapy and trazodone is among the pharmacological agents that have been used to manage the behavioral disturbances associated with cognitive dysfunction in patients with frontotemporal dementia [73] and Alzheimer's dementia [74]. Early and prompt treatment of behavioral disturbances could contribute to improving the quality of life of patients, their families, their caregivers and could reduce the overall health-care costs associated with the treatment of dementia.

10.8.1. Frontotemporal dementia

In this type of dementia progressive degeneration of the temporal and frontal lobes occurs and is characterized by varied symptoms and impairment in decision-making, behavioral control, emotion and language. Trazodone has been reported to decrease agitation and associated aggressive behaviors in patients with frontotemporal dementia [73].

10.8.2. Alzheimer's disease dementia

Trazodone decreased agitation and aggressive behaviors in some patient with and as a result, it lead to the reduction of caregivers' burden without modifying patients' cognitive functioning [74].

10.9. Sexual dysfunction

Reports of increased libido and sexual function in patients taking trazodone have led to its clinical use in patients with erectile dysfunction (ED) [75]. Trazodone was found to be beneficial in enhancing ED penile erection especially in men experiencing psychogenic ED [76].

The adjunctive use of trazodone could also reduce the SSRIs-induced sexual dysfunction and could also allow dose reduction of SSRIs without compromising their antidepressant efficacy in both male and female patients [2,4,77].

10.10. Pain conditions

Various antidepressants have been used in the treatment of pain conditions, including fibromyalgia, headache, neuropathy, back pain, and others. Although the exact mechanism by which antidepressants decrease pain remains unclear, their effect is not mediated solely through the alleviation of depressive symptoms [78]. Trazodone was found to be beneficial in reducing pain associated with migraine headache and in diabetic neuropathy [79,80]. In addition to trazodone effects on improving sleep quality, depression and anxiety, at the dose of 300 mg daily it was found to reduce pain intensity in patients with fibromyalgia [81]. Clinicians using trazodone for the treatment of pain conditions need to be aware of its decreased tolerability due to its adverse effects and that it could be beneficial at lower noninducing adverse effects doses as an adjunctive to other pain relieving agents [78].

10.11. Rehabilitation after acute ischemic stroke

It has been estimated that 25–60%of patients with stroke will develop poststroke depression (PSD) [82]. Patients with PSD who were treated with trazodone showed an improvement in their activities of daily living (ADL), a better functional outcome, less cognitive difficulties and decreased mortality when compared to patients who did not receive such a treatment [82].

Trazodone improved motor function and reduced disability following acute ischemic strokes [83]. Furthermore it was found to produce greater improvements in activities of daily living in patients with PSD [84].

The average daily doses of trazodone that are used in the treatment of various psychiatric and medical conditions as reported in the literature are summarized in Table 2.

Table 2. The average daily doses of trazodone for various psychiatric and medical conditions.

Conditions	Daily doses	References
Insomnia	25–100 mg at bedtime	[33]MEDLINE search of the literature published in English 1975–2003 [34]Retrospective, comparative study [35] A 3-week, within-subjects, randomized, double-blind, placebo-controlled design [36] Cross-sectional study [37]Sleep efficacy end points from randomized, placebo-controlled clinical trials in adult populations [38] MEDLINE search of the literature published in English 1980–2003
Anxiety disorders	Up to 300 mg given in three divided doses	[39] Data from a World Health Organization study, conducted in primary health clinics in 15 countries and two large population surveys [40] Critical appraisal of systematic reviews, clinical guidelines, and controlled trials [41] Single-blind trial [42] Data from 74 patients treated with placebo for 3 weeks and then blindly switched to active treatment for 8 weeks
Posttraumatic stress disorder	50–200 mg at bedtime for sleep Up to 400 mg given in two divided doses	[45] Survey of 74 patients admitted to a specialized 8 week inpatient treatment program for PTSD [46] Evidence obtained from randomized controlled trials
Obsessive compulsive disorder	Up to 300 mg given in three divided doses	[47] Case series report
Feeding and eating disorder	Flexible schedule, maximum 400 mg	[51] 23 consecutive cases of sleep-related eating disorder [52] A comparative study of disordered eating [53] Selective review of the literature
Substance use disorder	50–150 mg	[56] Double-blind, placebo-controlled study
Sleep difficulties during alcohol withdrawal	150–200 mg	[57] A national survey of addiction medicine physicians [58] A retrospective study
Cocaine induced foraging behaviors		[59] Review [60] Double-blind study [61]Case series
Behavioral disturbances	250 mg single or divided doses	[62]Systematic review of few randomized, controlled trials
Frontotemporal dementia Alzheimer's disease	50 mg every 12 h	[63]Naturalistic follow-up study
Sexual dysfunction	50–100 mg	[64] Systematic review and meta-analysis [65]Literature review [66] Preliminary open-label study
Pain conditions	100–200 mg divided doses	[68] Placebo-controlled crossover trial
Migraine headaches	50–100 mg	[69]Case series
Diabetic neuropathy Fibromyalgia	50–300 mg	[70]Open-label study
Rehabilitation after acute ischemic stroke	100–200 mg	[72] Cochrane systematic review [73] Double-blind trial

11. Conclusion

Trazodone is an antidepressant belonging to the SARI class of agents. It is approved by the FDA for the treatment of MDD. It has also shown some beneficial effects in the treatment of many psychiatric and medical conditions such as insomnia, anxiety disorders, posttraumatic stress disorder, obsessive compulsive disorder, feeding and eating disorders, substance use disorders, behavioral disturbances associated with cognitive dysfunction, sexual dysfunction, certain pain conditions, and rehabilitation after acute ischemic stroke.

Trazodone's beneficial effects and common use have been mainly based on few and small size clinical trials. More large, randomized placebo controlled double blind studies are necessary to demonstrate its efficacy in treating the many conditions for which it is used in clinical practice. Such studies would also need to demonstrate the risks and benefits ratio for the many non-FDA approved conditions for which trazodone has been prescribed. It is hoped that this review will provide mental health and primary care providers with the information that they need to feel comfortable in prescribing trazodone for various 'off label' psychiatric and medical conditions.

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