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DRUG EVALUATION

# Practical guidance for prescribing trazodone extended-release in major depression

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**ABSTRACT**

***Introduction***: Treatment of major depressive disorder aims for symptom remission and recovery of function, and involves a multifaceted approach including drug therapy, evidence-based psychotherapy, and electroconvulsive therapy, according to disease severity. Antidepressant monotherapy is generally the first-line approach for moderate to severe major depressive disorder (with or without psychotherapy). In some severe cases, patients may require the addition of antipsychotic therapy, electroconvulsive therapy, or antidepressant combination therapy.

***Areas covered***: This article examines the use of trazodone in major depressive disorder, with a focus on practical guidance regarding the use of trazodone extended-release (Contramid®).

***Expert opinion***: The extended-release once-a-day formulation of trazodone may provide a combination of efficacy and improved tolerability over other antidepressants and over the conventional immediate-release formulation.

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**KEYWORDS**
Major depressive disorder; treatment; trazodone; extended-release



## 1. Introduction

Depression represents a significant societal health burden, estimated to affect 350 million people worldwide; in terms of years lost to disability, depression is the leading cause of disability worldwide.[1] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines major depressive disorder as depressed mood or a significant loss of interest or pleasure in all or almost all activities for most of the day almost every day for 2 weeks, plus at least four of the following almost every day for 2 weeks [2]: significant weight loss in the absence of dieting or weight gain, change in appetite; insomnia or hypersomnia; fatigue or loss of energy; psychomotor agitation or retardation; feelings of worthlessness or excessive/inappropriate guilt; difficulty thinking or concentrating, or indecisiveness; and recurrent thoughts of death or suicidal ideation, suicide attempt, or developing a specific plan for committing suicide.

In 2004, major depressive disorder was the third highest in terms of worldwide burden of disease, but it is expected to become the leading burden by 2030.[3] Treatment of major depressive disorder aims for symptom remission and recovery of function, and involves a multifaceted approach including drug therapy, evidence-based psychotherapy, and electroconvulsive therapy, according to disease severity.[4–9] Antidepressant monotherapy is generally the first-line approach for moderate-to-severe major depressive disorder, with or without psychotherapy. In some severe cases, patients may require the addition of antipsychotic therapy, electroconvulsive therapy, or antidepressant combination therapy.

The treatment of major depressive disorder is complicated by the fact that many patients have no or only a partial response to antidepressant therapy, experience intolerable side effects, or relapse while on therapy.[10,11] Adherence to therapy is often poor in patients with mood disorders, but evidence suggests that adherence, and in some cases, efficacy, can be improved with the use of long-acting medications.[12–14]

Trazodone belongs to the serotonin antagonist and reuptake inhibitor class of drugs; it is well tolerated, with comparable efficacy to other second-generation antidepressants.[15] There are several formulations of trazodone, including immediate-release (IR) and extended-release (ER) tablets (Box 1, Table 1). This review summarizes the use of trazodone in major depressive disorder, with a focus on practical guidance

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**Box 1.** Drug summary.

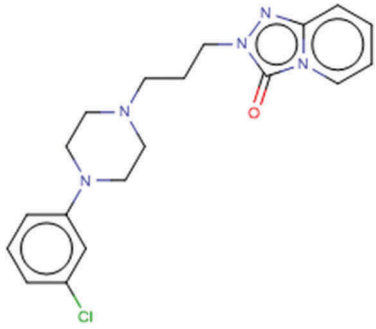
| | |
|---|---|
| Drug name (generic) | Trazodone extended release |
| Phase (for indication under discussion) | Launched |
| Indication (specific to discussion) | Major depressive disorder |
| Pharmacology description/ mechanism of action | Histamine H1 receptor antagonist<br>5 Hydroxytryptamine uptake inhibitor<br>Alpha 1 adrenoreceptor antagonist |
| Route of administration | Oral |
| Chemical structure |  |
| Pivotal trial(s) | Sheehan DV, Croft HA, Gossen ER, et al. Extended-release trazodone in major depressive disorder: a randomized, double-blind, placebo-controlled study. Psychiatry (Edgmont) 2009;6:20–33 [25] |

**Table 1.** Characteristics of single-dose trazodone IR compared with single-dose trazodone ER.[16–18]

| Parameter | Trazodone ER (300 mg) | Trazodone IR (100 mg) |
|---|---|---|
| $AUC_{0\text{-}t}$ (ng·h/mL) | 28.14 | 34.27 |
| $C_{max}$ (µg/mL) | 1.23 | 2.95 |
| $t_{max}$ (h) | 9.0 | 8.3 |
| $t½$ (h) | 11.8 | 8.3 |
| Drug delivery | Slowly rising and falling drug levels with sustained levels above the minimum antidepressant concentration | Delivers rapid unsustained drug levels |
| Dosing | Once daily to every three days | Multiple daily doses |

$AUC_{0\text{-}t}$: area under the plasma concentration–time curve from time 0 to the last quantifiable concentration; $C_{max}$: maximum observed plasma concentration; ER: extended-release; IR: immediate-release; $t_{max}$: the time required to reach $C_{max}$.

regarding the use of trazodone ER (Contramid®, Aziende Chimiche Riunite Angelini Francesco – ACRAF SpA, Rome, Italy).

### 1.1. Search strategy

For the literature search, the PubMed database was utilized; no date limits were applied. Keywords and search strings used were trazodone AND (extended-release OR prolonged-release) AND major depressive disorder; trazodone AND major depressive disorder; major depressive disorder.

## 2. Trazodone in major depressive disorder

Most guidelines [e.g. the American College of Physicians (ACP) Guideline on Second-Generation Antidepressants for Depression Treatment] recognize that there is insufficient evidence to recommend one second-generation antidepressant over another with regard to effectiveness, which does not differ among subgroups based on age, sex, race, or ethnicity. However, with regard to adverse events, the ACP guidelines recognize that bupropion has a lower rate of sexual adverse events compared with fluoxetine or sertraline, whereas paroxetine has increased rates of sexual dysfunction compared with fluoxetine, fluvoxamine, or sertraline. Also, the guidelines acknowledge that some antidepressants (including trazodone) may be more effective for the treatment of insomnia.[19]

The mechanism of action of trazodone has been previously reviewed.[16,17] Briefly, trazodone has a dual mechanism of action, inhibiting the serotonin transporter (SERT) and acting as a serotonin type 2 receptor ($5\text{-}HT_2$) antagonist (both $5\text{-}HT_{2A}$ and $5\text{-}HT_{2C}$). The action of trazodone against SERT and $5\text{-}HT_2$ is simultaneous. Trazodone also acts as a $\alpha_1$- and $\alpha_2$-adrenergic receptor and histamine $H_1$ receptor antagonist, and has minimal anticholinergic effects.

In clinical trials of patients with depression, trazodone has shown similar antidepressant efficacy to tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline (norepinephrine) reuptake inhibitors [16] when efficacy is measured using the Hamilton Depression Rating Scale (HAMD), the Clinical Global Impressions (CGI) Severity of Illness scale (CGI-S), and the Montgomery-Åsberg Depression Rating Scale (MADRS).[16]

Pharmacokinetic studies have shown that trazodone IR administration causes rapid peaks in drug levels, which then decline rapidly, and this occurs several times a day. This 'saw tooth' pattern results in drug levels much higher than required at some time points, as well as drug levels below the minimum required for efficacy at other points, which can cause sedation and lack of antidepressant efficacy, respectively.[17]

### 2.1. Trazodone ER

#### 2.1.1. Pharmacokinetics

Trazodone ER uses a proprietary drug delivery technology that ensures the controlled release of trazodone over 24 h.[16] This technology is based on a matrix of high amylose chemically crosslinked starch that is transformed by gastric fluids into a gel through which controlled drug diffusion occurs.[20] Pharmacokinetics

studies in healthy subjects have shown that the half-life of trazodone ER ranges from 12 to 13.2 h,[20] and the area under the concentration–time curve (AUC) and maximum plasma concentration ($C_{max}$) of a single dose of trazodone ER were ~20% and 60% lower than trazodone IR 100 mg administered three times over 24 h.[18] Multiple doses of trazodone ER (once daily for 7 days) were equivalent to trazodone IR three times daily with respect to AUC, but had a $C_{max}$ 43% lower.[18] Trazodone ER AUC and time to maximum plasma concentration were not affected by food; $C_{max}$ was increased 86% versus fasting conditions after a high-fat meal.[18] Trazodone ER exhibits linear pharmacokinetics over the dose range of 75–375 mg when administered under fasting conditions.[20]

The gradual release of trazodone ER maintains blood levels above the minimum antidepressant concentration required for efficacy, but avoids the spikes in concentration seen with trazodone IR, suggesting that peak dose side effects should be lower with trazodone ER than trazodone IR, but efficacy should be comparable.[17]

### 2.1.2. Efficacy and safety

Four studies have investigated the use of trazodone ER in major depressive disorder (Table 2). Two were randomized, double-blind, placebo-controlled studies, one a multicenter study of 412 patients in the US and Canada,[21] and the other a study of 363 Chinese patients.[22] Two were randomized, double-blind, multicenter active comparator studies in Europe: a study of 108 patients investigating trazodone ER 150–450 mg/day versus paroxetine 20–40 mg/day,[23] and a study of 122 patients who received trazodone ER 150–450 mg/day or sertraline 50–100 mg/day.[24]

#### 2.1.2.1. Efficacy in depression.

The placebo-controlled studies showed that trazodone ER was significantly better at improving the 17-item HAMD versus placebo ($p \leq 0.012$; Table 2).[21,22] The efficacy of trazodone ER versus placebo occurred early, with the difference between treatment groups evident at week 1 in both studies. Generally, response and remission rates were higher with trazodone ER than with placebo. Of interest, a greater decrease in the change from baseline in the HAMD-17 depressed mood item (item 1) was observed for trazodone patients, thus suggesting that the antidepressant effect is not exclusively accounted for by the improvement in the sleep-related items.[25]

In the Chinese study, trazodone ER demonstrated sustained antidepressant efficacy with significantly greater improvements in HAMD-17 total score at 1, 2,

Table 2. Summary of clinical trials investigating trazodone ER.

| Study | Study design; duration | Patients | Treatments (n) | Primary efficacy end point | Primary efficacy results |
|---|---|---|---|---|---|
| *Placebo controlled* | | | | | |
| Sheehan et al. [21] | Randomized, double-blind, multicenter; 8 weeks | Adults with MDD and a MADRS total score of ≥26; current MDD episode duration of ≥1 month | TRZ ER 150–375 mg/day (206)<br>PL (206) | ΔHAMD-17 total score from BL | TRZ: −11.4*<br>PL: −9.3 |
| Zhang et al. [22] | Randomized, double-blind, multicenter, flexible dose; 6 weeks | Chinese patients with MDD and a HAMD-17 score of ≥18 | TRZ ER 150 mg BID (183)<br>PL (180) | ΔHAMD-17 total score from BL | TRZ: −11.07**<br>PL: −8.29 |
| *Active comparator* | | | | | |
| Kasper et al. [23] | Randomized, double-blind, multicenter; 6 weeks | Adults with MDD, a HAMD-17 score of 18–24 and a MADRS score of <30; depression symptoms for ≥1 month | TRZ ER 150 mg BID (55)<br>PAR IR 20 mg OD (53) | CGI-S<br>CGI-GI<br>ΔHAMD from BL<br>ΔMADRS from BL | Similarly improved in both groups<br>Similarly improved in both groups<br>TRZ: −14.6<br>PAR: −15.0<br>TRZ: −18.3<br>PAR: −18.4 |
| Munizza et al. [24] | Randomized, double-blind, multicenter; 6 weeks | Adults with MDD, a HAMD-17 score of 18–24 and a MADRS score of <30; depression symptoms for ≥1 month | TRZ ER 150 mg BID (62)<br>SERT 50 mg OD (60) | CGI-S<br>CGI-GI<br>ΔHAMA from BL<br>ΔHAMD from BL<br>ΔMADRS from BL | Similarly improved in both groups<br>Similarly improved in both groups<br>Similarly improved in both groups<br>TRZ: −12.9<br>SERT: −11.5<br>TRZ: −16.5<br>SERT: −15.0 |

*$p < 0.05$; **$p < 0.001$ vs. placebo.

BID: twice daily; BL: baseline; CGI-GI: Clinical Global Impressions-Global Improvement scale; CGI-S: Clinical Global Impressions-Severity of Illness scale; ER: extended-release; HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Scale; IR: immediate-release; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; OD: once daily; PAR: paroxetine; SERT: sertraline; TRZ: trazodone;.

3, and 6 weeks of double-blind therapy compared with placebo ($p < 0.05$ for all time points). Response rates in the trazodone ER and placebo groups were 59.6% and 37.2% ($p < 0.001$ between groups), while significantly more patients receiving trazodone than placebo achieved remission (35.5% vs. 22.2%; $p = 0.005$). In the US/Canadian study, significantly greater absolute mean improvements in HAMD-17 scores were noted with trazodone ER (11.0 vs. 8.6; $p = 0.0002$). Remission rates were not significantly different with trazodone ER versus placebo (35.6% vs. 31.9%; $p = 0.22$), but there were significantly more responders receiving trazodone ER than placebo (54.0% vs. 41.2%; $p = 0.003$).

The reduction in depression symptoms and the proportion of patients with a response was similar between trazodone ER and paroxetine and sertraline in the active comparator studies.[23,24] Compared with both paroxetine and sertraline recipients, trazodone ER results in similar improvements in the CGI-S and the CGI-Global Improvement scales, and similar reductions from baseline in HAMD total scores, Hamilton Anxiety scale scores, and MADRS scores (Table 2). Approximately 75% of trazodone ER recipients versus ~65% of sertraline recipients were considered responders, and ~60% and 49% of patients achieved remission.[24] According to HAMD response, 87% and 91% of trazodone ER and paroxetine recipients responded to therapy, and 69% and 68% achieved remission.[23] Onset of antidepressant efficacy was faster for paroxetine compared with trazodone, although this difference was not evident at 6 weeks.[23] While a similar onset of antidepressant efficacy was reported for trazodone and sertraline, trazodone displayed more rapid onset of anxiolytic activity, possibly due to its sedative effects, an effect that was not sustained after 3 weeks of treatment.[24]

Of note, following an increase in antidepressant dose, a greater proportion of trazodone nonresponders (after 3 weeks treatment) showed remission at the end of the study compared to those treated with paroxetine. Comparative data with paroxetine suggest that some patients benefit from the higher trazodone dose and achieve remission, while dose increases in paroxetine may not achieve this effect. Therefore, dose increases of trazodone to 450 mg daily should be considered in nonresponders, while taking care to ensure an adequate period of dose titration to reduce the occurrence of adverse effects.

*2.1.2.2. Effect on sleep parameters.* Insomnia has been reported in >90% of patients with major depressive disorder,[21] but clinical trials of trazodone show a beneficial effect of the drug on sleep measures in these patients.[16] In both placebo-controlled studies of trazodone ER, measures of sleep quality were improved with trazodone ER versus placebo [21,22]; in one study, trazodone ER improved overall sleep quality and the number of nighttime awakenings, and decreased the proportion of patients who had trouble falling asleep, [21] while in the other study, the decreases from baseline in Pittsburgh Sleep Quality Index total score were significantly greater in the trazodone ER group versus the placebo group (−6.4 vs. −4.5; $p < 0.001$).[22] Furthermore, there was a trend toward a greater proportion of patients rating their overall sleep quality as good or excellent with trazodone ER compared with placebo.[21]

The rate of sleep disorders were also significantly reduced with trazodone ER therapy versus paroxetine and sertraline.[23,24] After 6 weeks of treatment, the mean sleep score for trazodone ER recipients was significantly ($p < 0.05$) better than that for paroxetine recipients.[23] The sleep disturbance factor of the HAMD score was significantly ($p < 0.05$) more favorable in patients receiving trazodone ER than sertraline.[24]

*2.1.2.3. Tolerability.* In the placebo-controlled studies, adverse events seen with trazodone ER were as expected for trazodone and were mostly mild to moderate in intensity.[21,22] Serious adverse events occurred at a similar rate with trazodone ER and placebo (Table 3). Where reported, more patients receiving trazodone ER discontinued therapy compared with placebo recipients; frequent adverse events that occurred more often with trazodone than placebo included dizziness, dry mouth, headache, nausea, and somnolence (Table 3).[21,22] These events had an early onset but were transient in the majority of patients; dizziness had a mean onset of 6.7 days and a median duration of 4 days, somnolence had a mean onset of 7.6 days and a median duration of 9 days, and sedation occurred with a mean onset of 6.1 days and a median duration of 12.5 days.[21] These adverse events may be of particular concern in the elderly, who are more likely to be using multiple medications and who are at greater risk of falls. Similarly, sedation that may impair driving is also possible when initiating or titrating treatment with trazodone ER or when used in combination with other potentially sedating drugs, such as benzodiazepines.[26]

Patients receiving trazodone ER in the active-controlled studies experienced adverse events related to the central nervous system, while those receiving paroxetine or sertraline experienced mainly gastrointestinal events.[23,24] Common adverse events in both groups included headache, insomnia, nausea, and dry mouth, with rates varying between studies (Table 3).

Table 3. Adverse events seen with trazodone ER versus comparator in the placebo- and active-controlled studies.

| | Placebo-controlled studies | | | | Active-controlled studies | | | |
|---|---|---|---|---|---|---|---|---|
| | Sheehan et al. [21] | | Zhang et al. [22] | | Kasper et al. [23] | | Munizza et al. [24] | |
| Parameter | TRZ CD (n = 202) | PL (n = 204) | TRZ ER (n = 185) | PL (n = 181) | TRZ ER (n = 55) | PAR (n = 53) | TRZ ER (n = 62) | SERT (n = 60) |
| Overall AEs, n (%) | 181 (89.6) | 164 (80.4) | 100 (54.1) | 56 (30.9) | 19 (35) | 14 (26) | 26 (41.9) | 26 (43.3) |
| Discontinuations due to AEs, n | 25 | 6 | NR | NR | 3 | 0 | 2 | 6 |
| Serious AEs, n | 3 | 2 | NR | NR | 0 | 0 | 3[a] | |
| Severe AEs, n | NR | NR | 1 | 0 | 0 | 0 | 3 | 3 |
| Deaths, n | 0 | 1 | NR | NR | 0 | 0 | 0 | 0 |
| *Most frequent AEs (>5% of patients in any group), n (%)* | | | | | | | | |
| Back pain | 11 (5.4) | 7 (3.4) | – | – | – | – | – | – |
| Blurred vision | 11 (5.4) | 0 | – | – | – | – | – | – |
| Constipation | 16 (7.9) | 4 (2.0) | – | – | – | – | – | – |
| Diarrhea | 19 (9.4) | 23 (11.3) | – | – | – | – | 2 (3.3) | 3 (4.8) |
| Dizziness | 50 (24.8) | 25 (12.3) | 37 (20)* | 13 (7.2) | – | – | 12 (20) | 8 (12.9) |
| Dry mouth | 51 (25.2) | 26 (12.7) | 20 (10.8) | 13 (7.2) | 0 | 4 (7.5) | 3 (5.0) | 2 (3.2) |
| Fatigue | 30 (14.9) | 17 (8.3) | – | – | – | – | – | – |
| Headache | 67 (33.2) | 55 (27.0) | 10 (5.4) | 4 (2.2) | 4 (7.3) | 0 | 1 (1.7) | 5 (8.1) |
| Hypersomnia | – | – | – | – | 3 (5.5) | 0 | – | – |
| Insomnia | – | – | – | – | 3 (5.5) | 3 (5.7) | 3 (5.0) | 3 (4.8) |
| Nausea | 42 (20.8) | 26 (12.7) | 11 (5.9) | 5 (2.8) | 1 (1.8) | 6 (11.3) | 6 (10) | 9 (14.5) |
| Sedation | 34 (16.8) | 7 (3.4) | – | – | – | – | – | – |
| Somnolence | 63 (31.2) | 32 (15.7) | 20 (10.8)* | 2 (1.1) | – | – | 5 (8.3) | 3 (4.8) |
| Stomachache | – | – | – | – | – | – | 0 | 3 (4.8) |
| Tremor | – | – | – | – | – | – | 3 (5.0) | 1 (1.6) |
| Vomiting | – | – | – | – | – | – | 3 (5.0) | 2 (3.2) |

[a]Treatment group not specified.
*$p < 0.001$ vs. placebo.
AEs: adverse events; CD: Contramid; ER: extended-release; NR: not reported; PAR: paroxetine; SERT: sertraline; TRZ: trazodone.



Serious or severe adverse events were either not seen or occurred at a similar rate between trazodone ER and the active comparator; more patients in the trazodone ER group discontinued due to adverse events than paroxetine, but fewer patients in the trazodone ER group discontinued for the same reason versus sertraline (Table 3). Given that trazodone may enhance the response to alcohol, barbiturates, and other central nervous system depressants, such as opioid analgesics, the medication should not be used in combination with such substances/medications.

## 2.2. Trazodone ER in clinical practice

### 2.2.1. Labeling information

Trazodone ER is approved for use in the treatment of major depressive disorder in adults, both in the US [26] and in Italy.[27] It should not be used in children or adolescents because in clinical trials of the use of antidepressants in children and adolescents patients demonstrated an increased frequency of suicidal behaviors and hostility.[26,27]

The recommended dosage differs between countries: in the US, the starting dose is 150 mg once daily, to be increased by 75 mg/day every three days if required, to a maximum dose of 375 mg/day,[26] while in Italy, the recommended starting dose is 75–150 mg/day, to be increased by 75 mg/day every three days if required, to a maximum dose of 300 mg/day.[27] Generally, it is recommended that patients be treated with trazodone ER for several months; maintenance treatment should be administered at the lowest effective dose, and patients should be regularly assessed to determine whether maintenance treatment is still required.[26] If trazodone treatment is to be discontinued, the dose should be tapered over time, and patients monitored for withdrawal symptoms.[26,27]

Warnings and precautions associated with trazodone ER include potential clinical worsening and suicide risk, requiring close monitoring of patient behavior by families, caregivers, and physicians.[26,27] Patients receiving trazodone ER, particularly in combination with serotoninergic drugs, drugs affecting serotonin metabolism, antipsychotics or dopamine agonists, may develop serotonin syndrome or neuroleptic malignant syndrome.[26,27] There is potential for QT prolongation and sudden death,[26,27] cognitive and motor impairment, abnormal bleeding, orthostatic hypotension and syncope, and development of hyponatremia in patients receiving trazodone ER.[26] Trazodone is not recommended for patients recovering from myocardial infarction, and patients with cardiac disease receiving trazodone ER should be closely monitored.[26] Other patients who should be closely monitored while receiving trazodone include patients with epilepsy or hypothyroidism, and those with liver or kidney failure.[27] Trazodone ER should be used

with caution in men with conditions predisposing them to priapism or men with penile deformation.[26] Trazodone should be discontinued immediately if priapism develops.[27]

Trazodone ER may interact with the following drugs: monoamine oxidase inhibitors; cytochrome P450 inhibitors/inducers; tricyclic antidepressants; fluoxetine; phenothiazines; anesthetics and muscle relaxants; digoxin and phenytoin; serotonergic drugs; nonsteroidal anti-inflammatory drugs, aspirin, or drugs associated with coagulation or bleeding; and warfarin.[26] Concomitant use of trazodone with drugs associated with cardiac toxicity or agents that prolong the QT interval should be avoided due to the potential increased risk for ventricular arrhythmias.[16,21]

Trazodone ER should be used in pregnant and nursing women only if the benefit justifies the potential risk to the baby.[26,27] It should be used with caution in patients older than 65 years and those with hepatic and renal impairment.[26,27]

## 2.3. Case report

This case describes the use of trazodone in a patient with major depressive disorder, insomnia and concomitant symptoms of anxiety and irritability. Some aspects were modified for didactic purpose and to protect patient's anonymity.

### 2.3.1. Case description

Ms. V is a 36-year-old single white woman who presented at our clinic with depressed mood. She reports that in the previous weeks she has felt sad, 'down in the dumps', anxious, and unable to enjoy the things she used to enjoy. She also reports difficulty falling asleep, problems with sleep continuity and early morning awakenings, irritability, as well as decreased motivation and difficulty concentrating. She frequently becomes upset and yells and screams whenever something unfair happens. She also describes tearfulness, decreased level of energy, feelings of worthlessness and excessive guilt, racing thoughts at night, distractibility, diminished concentration, and increased indecisiveness. She claims not to have periods of elevated mood, increased goal-directed activity, reduced need for sleep, or an adequate number of manic symptoms fulfilling a diagnosis for a manic episode.

Ms. V is normal weight for her age/height but describes herself as being very worried of gaining weight. She admits to experiencing at least three similar episodes in the past, lasting approximately 6 months each. She reports occasional thoughts of death and ideas that life is not worth living but denies any active suicidal ideation or plan. She claims to have no current or past drug abuse but reports of period in which she could not stop using benzodiazepines.

Because of her current symptoms, she has been unable to properly function at work and has been stressed.

She denies any major concomitant physical illness but reports mild/moderate constipation. Both physical examination and laboratory investigations are normal, other than for moderately elevated cholesterol. Her family history is positive for depression, generalized anxiety disorder, and possibly bipolar disorder. The family history is negative for suicide.

### 2.3.2. Diagnostic assessment

The patient was diagnosed with major depressive episode in major depressive disorder. The hypomanic features did not seem to meet the threshold for a hypomanic episode, but we noted the possible presence of a hypomanic features specifier (according to the recently issued DSM-5). DSM-5 replaced the diagnosis of 'mixed episode' with a mixed-features specifier that can be applied to episodes of major depression, hypomania, or mania. In order to be diagnosed with the new specifier in the case of major depression, the DSM-5 requires the presence of at least three manic/hypomanic symptoms that do not overlap with symptoms of major depression. However, no treatment recommendations have been issued yet for these cases.

### 2.3.3. Treatment considerations

Ms. V presented with a relatively typical presentation of depression with anxiety features and isolated hypomanic symptoms. It is common that the manic/hypomanic symptoms do not meet the threshold for a manic/hypomanic episode, but the diagnostic criteria for a depressive episode are fully met.

In light of the subthreshold manic symptoms, consideration was given to the use of a mood stabilizer. However, she had no personal nor family history of full-blown manic or hypomanic episodes, she did not endorse and early age of onset of mood episodes, nor a history of postpartum depression or a high number of mood episodes, and the current manic symptoms were very mild and not considered to be particularly dangerous. Also, the patient had concerns about adverse effects associated with medication, with special reference to weight gain. Given the tolerability of mood stabilizers is usually lower than the tolerability of many antidepressants, a stabilizer was not initiated but was considered for future use in the event that manic/agitation symptoms worsened.

The initial decision was that trazodone would be appropriate, provided that a mood stabilizer or antimanic agent be rapidly added in case of a worsening of the mixed symptomatology. We selected trazodone due to its efficacy in depression, insomnia, and anxiety and due to antagonism at receptors $5HT_{2A}$ and $5HT_{2C}$, which helps to overcome the tolerability issues that are often associated with second-generation antidepressants such as SSRIs (i.e. insomnia, anxiety and sexual dysfunction). Benzodiazepines were avoided because of the patient's likely history of abuse, as were tricyclic antidepressants (TCAs, such as trimipramine) and mirtazapine because of tolerability considerations.

#### 2.3.4. Clinical course following the initiation of treatment

Trazodone Contramid® was started at 150 mg at night. After 2 days of treatment, Ms V reported improvements in symptoms of insomnia, anxiety and irritability. She also reported mild and tolerable drowsiness and lightheadedness, which disappeared by day 7, without the need to change trazodone dose. At that time, her depressive and anxiety symptoms were improved but still present. The dose of trazodone was increased to 225 mg (one and a half 150 mg tablets) at night. No major adverse events were noted. By week 4, anxiety and nervousness were reported to be much better, albeit not completely cleared. A further dose increase (to 300 mg taken at night) was implemented and by week 5, all of the patient's symptoms cleared.

#### 2.3.5. Comments

This case illustrates the successful use of trazodone to improve the symptoms of depression, anxiety, insomnia, irritability and mild/isolated manic symptoms (that were insufficient to reach the threshold for a bipolar disorder diagnosis) a patient with recurrent major depressive disorder. At doses of 150–300 mg, trazodone produced clear antidepressant effects and maintained the favorable effects on symptoms such as insomnia, anxiety and irritability. The recently approved prolonged release formulation (Contramid®), which may be started at a dose (150 mg) that is already in the antidepressant range and is usually well tolerated, permits a further optimization of the benefits offered by this medication.

In this case report, trazodone proved effective, was not associated to significant/long lasting adverse effects and was successfully improved anxiety and irritability concomitant to depression.

### 2.4. Conclusions

Trazodone is a well-established antidepressant therapy with good tolerability and a comparable efficacy profile to other antidepressants. The trazodone ER formulation allows for sustained release of drug over a 24-hour period, avoiding peaks and troughs in drug concentration and allowing for once-a-day dosing. The efficacy of trazodone ER in both clinical trials and the clinical practice setting has been established and trazodone ER may be particularly useful in patients with major depressive disorder and concomitant symptoms of insomnia, anxiety, irritability or agitation.

## 3. Expert opinion

Although relatively widely used, in current clinical practice trazodone is more likely to be prescribed as a sedative hypnotic than as an antidepressant.[9] However, a number of head-to-head trials have been conducted between trazodone (dose range 150–450 mg) and second-generation antidepressants in patients with major depressive disorder. An analysis of these head-to-head trials showed that the relative benefit, in terms of response, was comparable between trazodone and other second-generation antidepressants.[28] Indeed, several head-to-head studies have demonstrated the comparable antidepressant efficacy between trazodone and other drug classes, including SSRIs (fluoxetine, paroxetine, sertraline, citalopram, and escitalopram), serotonin–norepinephrine reuptake inhibitors (venlafaxine and mirtazapine), noradrenaline and dopamine reuptake inhibitors (bupropion), and tricyclic antidepressants (amitriptyline and imipramine).[16]

The recent development of a new ER once-a-day formulation of trazodone may provide a combination of efficacy and improved tolerability over other antidepressants and over the conventional IR formulation of trazodone. As with most approved medications, trazodone has several benefits and some potential risks/disadvantages. A number of clinically frequent and/or relevant problems have been encountered with trazodone. Trazodone is unlikely to be effective for the subtypes of depression characterized by hypersomnia, low energy, and psychomotor retardation. There is also the risk of orthostatic hypotension or sedation, although this is not observed as frequently with the ER formulation as with the IR formulation. Concomitant use of trazodone with drugs known to exert cardiac toxicity or to prolong the QT interval should be avoided because it could increase the risk of ventricular arrhythmias, including torsade de pointes. Rare cases of life-threatening cardiac arrhythmias, including ventricular

tachycardia, have been reported in clinical and preclinical studies. Trazodone may also be associated with rare occurrences of priapism. For this reason, trazodone should be used with caution in men who have conditions that might predispose them to priapism (e.g. sickle cell anemia, multiple myeloma, leukemia, autonomic nervous system dysfunctions, and hypercoagulable states), or in men with anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, or Peyronie's disease).

In our experience, trazodone ER has a number of advantages. It may be started at a dose (150 mg) that is already potentially effective as an antidepressant and that can be titrated up to 225 mg first and to 300 mg afterwards, every 3–4 days. The reduced peak blood levels of trazodone achieved with this formulation usually mitigate tolerability issues, such as sedation and orthostatic hypotension. Trazodone antagonism at receptors $5HT_{2A}$ and $5HT_{2C}$ helps to overcome the tolerability issues that are often associated with second-generation antidepressants such as SSRIs (i.e. insomnia, anxiety, and sexual dysfunction). Furthermore, it is effective for those subtypes of depression that include symptoms such as insomnia, anxiety, and/or irritability or agitation. Although it has not been scientifically tested for bipolar depression, we have found this medication particularly useful in a number of patients with that condition. Unlike the benzodiazepines, trazodone is unlikely to be abused or induce dependence/tolerance, and it is not usually associated with anticholinergic adverse effects, such as those observed with the tricyclic antidepressants. Finally, unlike mirtazapine, trazodone does not usually increase body weight. In summary, we believe that trazodone is an effective antidepressant that may overcome the tolerability issues that are often associated with second-generation antidepressants such as SSRIs (i.e. sexual dysfunction, insomnia, and anxiety). We also believe that the development of the prolonged-release once-a-day Contramid formulation of trazodone (TzCOAD) may add further benefits to the efficacy and tolerability profile of this antidepressant, which has been primarily used as a hypnotic but which may now see a resurgence of interest for the management of patients with major depressive disorder. However, we also believe that more studies are needed to confirm the results of the only large, double-blind, placebo-controlled trial on TzCOAD, which has been published to date.[21]

## Declaration of interest

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• of interest
•• of considerable interest

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