

Rassegna

Clinical guidance for the use of trazodone in major depressive disorder and concomitant conditions: pharmacology and clinical practice

Guida clinica per l'uso del trazodone nel disturbo depressivo maggiore e nelle condizioni concomitanti: farmacologia e pratica clinica

ALESSANDRO CUOMO^{1,2*}, ANDREA BALLERINI³, AMALIA CECILIA BRUNI⁴, PAOLO DECINA⁵, GUIDO DI SCIASCIO⁶, ALESSIO FIORENTINI⁷, FRANCESCO SCAGLIONE⁸, CLAUDIO VAMPINI⁹, ANDREA FAGIOLINI¹

*E-mail: alessandrocuomo86@gmail.com

¹Dipartimento di Medicina Molecolare e dello Sviluppo, Università di Siena

²Divisione di Psichiatria, Sistema Sanitario Nazionale della Lombardia, Mantova

³Sod di Psichiatria, Azienda Ospedaliero-Universitaria Careggi, Firenze

⁴Centro Regionale di Neurogenetica, Lamezia Terme, Azienda Sanitaria Provinciale di Catanzaro

⁵Private practice

⁶Dipartimento di Salute Mentale, ASL Bari

⁷Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano

⁸Dipartimento di Oncologia ed Emato-oncologia, Università di Milano

⁹Servizio di Psichiatria e Psicogeriatrics, Clinica San Francesco, Verona

SUMMARY. Aim. To provide a review of the clinically relevant evidence pertaining to the use of trazodone in major depressive disorder. **Methods.** Medline and Cochrane Library searches were searched using the keywords 'trazodone' AND 'depression', to identify the most relevant literature pertinent to the pharmacological properties of trazodone and its use in clinical practice. Articles that were selected included basic pharmacology papers, clinical trials, clinical practice guidelines, and reviews. Related references were cross checked. European and United States prescribing information was reviewed as well. An effort was made to give weight to the information that was most relevant for daily clinical practice. **Results.** Trazodone is an antidepressant with a mechanism of action that remains innovative and with a favorable profile for the treatment of depression. The appropriate antidepressant doses are usually 150-300 mg/day and are often higher than the doses that are used when trazodone is prescribed to augment the antidepressant effect of another medication, for instance when trazodone is prescribed to address insomnia in a patient treated with an SSRI. Trazodone is usually well tolerated and has a low risk of anticholinergic side effects, weight gain and sexual side effects. **Discussion.** Trazodone is an established medication that is efficacious for the treatment of a broad array of depressive symptoms, including symptoms that are less likely to respond to other antidepressants (e.g. SSRI), such as insomnia. As an antidepressant, trazodone has proven as efficacious as the tricyclic and second-generation antidepressants and is tolerated relatively well. Trazodone may be helpful for patients with major depression and comorbid insomnia, anxiety or psychomotor agitation. **Conclusions.** Trazodone is efficacious antidepressants with a relatively low risks of side effects such as weight gain, sexual or anticholinergic effects (such as constipation, urinary retention, dry mouth). In addition to being able to control a wide range of depressive symptoms, trazodone may improve sleep and be particularly helpful for patients whose symptoms of depression include insomnia.

KEY WORDS: trazodone, depression, insomnia, anxiety, agitation, oral, intramuscular, intravenous, contramid.

RIASSUNTO. Scopo. Fornire una revisione delle informazioni clinicamente rilevanti relative all'uso del trazodone nel disturbo depressivo maggiore. **Metodi.** Sono state eseguite ricerche su Medline e Cochrane Library usando le keyword 'trazodone' AND 'depression', per identificare la letteratura più pertinente alla revisione delle proprietà farmacologiche del trazodone e al suo uso nella pratica clinica. I documenti selezionati hanno incluso studi di farmacologia di base, studi clinici, linee guida, revisioni, schede tecniche e bibliografia correlata. Particolare attenzione è stata dedicata all'estrazione delle informazioni più rilevanti per la pratica clinica quotidiana. **Risultati.** Trazodone è un antidepressivo consolidato, con un meccanismo di azione ancora innovativo e con un favorevole profilo di efficacia, per il trattamento della depressione. Le dosi antidepressive appropriate sono solitamente 150-300 mg/die e sono spesso superiori alle dosi che vengono utilizzate quando trazodone sia invece prescritto per potenziare l'effetto antidepressivo di un altro farmaco, per es., per trattare l'insonnia in un paziente depresso trattato con un SSRI. Trazodone è generalmente ben tollerato e ha un basso rischio di effetti collaterali anticolinergici, di aumento di peso e di effetti collaterali sessuali. **Discussione.** Trazodone è efficace per il trattamento di una vasta gamma di sintomi depressivi, compresi quelli che hanno meno probabilità di rispondere ad altri antidepressivi (per es., SSRI), come l'insonnia. Per il trattamento della depressione, l'efficacia di trazodone è risultata simile a quella degli antidepressivi triciclici e di seconda generazione e la sua tollerabilità è di solito buona. Trazodone può essere utile per i pazienti con depressione maggiore e insonnia, ansia o agitazione psicomotoria. **Conclusioni.** Trazodone è un antidepressivo efficace con un rischio relativamente basso di effetti collaterali come aumento di peso, disfunzioni sessuali o effetti anticolinergici (come stitichezza, ritenzione urinaria, secchezza delle fauci). Oltre a essere in grado di controllare una vasta gamma di sintomi depressivi, trazodone è efficace per migliorare il sonno e può essere particolarmente utile per i pazienti i cui sintomi di depressione includono l'insonnia.

PAROLE CHIAVE: trazodone, depressione, insonnia, ansia, agitazione, somministrazione orale, somministrazione intramuscolo, somministrazione intravenosa, contramid.

INTRODUCTION AND HISTORICAL BACKGROUND

Trazodone is an established medication, developed in the 1960s by Angelini Research Laboratories, as a second-generation antidepressant characterized by a mechanism of action (MOA) that remains innovative¹. Trazodone MOA is different from the MOA of the antidepressants that preceded (e.g. tricyclic antidepressants - TCA) and followed (e.g. SSRIs, SNRIs, atypical antidepressants) its development. Trazodone efficacy has been attributed to its properties as a serotonin antagonist and reuptake inhibitor (SARI) and clinical trials have clearly confirmed its efficacy as an antidepressant¹. Trazodone resulted as efficacious as the tricyclics (TCA) and second-generation antidepressants, with a relatively favorable tolerability profile². Trazodone spectrum of action includes symptoms that are less likely to respond to other antidepressants (e.g. SSRIs), such as insomnia¹. To date, there are several formulations of trazodone, including immediate release (Tz-IR), delayed release (Tz-RP-AC), and extended-release-contramid (Tz-ER-COAD) tablets, as well as liquid formulations, such as the 60 mg/ml liquid solution (Tz-drops) and the intramuscular- intravenous-solution^{3,4}. This manuscript summarizes the use of trazodone in major depressive disorder (MDD), which is the indication for which the medication is approved in adults from the United States Food and Drugs Administration (FDA) and the European Medicines Agency (EMA), with a focus on its clinical pharmacology and the goal to provide practical guidance on issues such as patients' selection (e.g. prescribing trazodone to those patients who can benefit the most from this medication), initial treatment (e.g. choosing the appropriate starting dose and titration schedule), sequential treatment (e.g. switching from intramuscular or intravenous formulation to one of the oral formulations) as the clinical picture improves/changes over time. We also review the available information about trazodone efficacy on symptoms or diseases that often present in comorbidity with major depressive disorder (MDD), to evaluate the potential benefits of this medication when it is prescribed for its in label indication (MDD) in patients who are also affected by other diseases.

METHODS

Medline and Cochrane Library were searched using the key words 'trazodone' AND 'depression'. European, Canadian, and United States prescribing information were reviewed as well. Articles that were selected included basic pharmacology papers, clinical trials, clinical practice guidelines, and reviews. Related references were cross checked. Articles were then selected with the goal to give weight to the information that was most relevant for daily clinical practice

PHARMACOLOGICAL PROPERTIES

Mechanism of action

Trazodone is classified as a serotonin antagonist-reuptake inhibition (SARI)⁵. Preclinical studies have shown that trazodone selectively inhibits neuronal reuptake of serotonin (Ki=367 nM) and acts as an antagonist at 5-HT-2A (Ki=35.6

nM) serotonin receptors. Of note, trazodone ability to block serotonin transporters is 100 fold less potent than the ability to block 5-HT2A receptors.

Other clinically relevant pharmacologic actions include antagonism at several other monoaminergic receptors including 5-HT2B (Ki=78.4 nM), 5-HT2C (Ki=224 nM), α 1A (Ki=153 nM), α 2C (Ki=155 nM) and partial agonism at 5HT1A (Ki=118 nM) receptor^{5,6} whereas the anticholinergic effects are minimal^{1,5,6}. Trazodone is a dose dependent multi-functional psychotropic drug. At low doses, trazodone mainly acts at 5-HT2A, H1 and α 1 receptors, and primarily works as a sedative-hypnotic medication⁵. Once the dose is raised 3-5 fold to reach a level able to block the of serotonin transporter (SERT), trazodone becomes an antidepressant^{1,5}. A recent study⁷, estimated that the occupancy for SERTs is predicted to be 86% when trazodone is administered at 100 mg daily and 90% when trazodone is given at 150 mg daily. At these doses trazodone almost completely blocks the 5-HT2A and 5-HT2C receptors. The authors noted that the fact that higher doses of trazodone are more effective than lower doses in treating depression, suggests that – for the treatment of depression – the blockage of SERT (that is significantly achieved with higher doses) is likely more important than the block of alpha-2 adrenoreceptor, 5-HT2A and 5-HT2C receptors, or the stimulation of 5-HT1A receptor, which are occupied already at lower doses. As mentioned above, unlike SSRIs and SNRIs, trazodone is associated with simultaneous inhibition of serotonin transporter and 5-HT2A and 5-HT2C receptor antagonism, which contributes to trazodone's antidepressant efficacy and increases its tolerability, by reducing the risk insomnia, sexual dysfunction and anxiety that are often associated with 5-HT2A/2C stimulation^{1,5}. Alpha2 (α 2) antagonism may also contribute to the antidepressant effect, while the antagonistic properties at alpha1, alpha2 -adrenergic and H1 receptors contribute to trazodone sleep-inducing effect, which may be further enhanced by the 5-HT2A antagonism^{1,5}. Unlike SSRIs, trazodone does not induce an apathy syndrome. The exact etiology of SSRI-induced indifference remains unknown. However, it is suggested that this syndrome may be related to 1) serotonergic stimulation and/or 2) serotonergic modulation of mid-brain dopaminergic systems, which project to the prefrontal cortex⁸. At these sites, the overstimulation of 5-HT2A induces the release of GABA which in turn inhibits the release of dopamine and induces indifference. The 5HT2A antagonism of trazodone prevents this phenomenon.

Pharmacokinetics

Absorption

Trazodone hydrochloride is well absorbed after oral administration with peak plasma levels obtained within one-half to two hours after ingestion. Absorption is somewhat delayed and enhanced by food. Trazodone is 89-95% protein bound in vitro at concentrations attained with therapeutic doses^{3,6,9}. Contramid, is a drug delivery technology based on cross-linked, high amylose starch. Following oral ingestion, gastric fluids transform the surface of a Contramid based product into a semi-permeable membrane that stabilizes rap-

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idly and regulates the release of the drug. Contramid technology contained within the controlled-release trazodone tablet is designed to avoid peak blood levels of trazodone associated with multiple administrations of immediate-release formulations and to maintain stable plasma concentrations of the drug at levels that are high enough to provide antidepressant effects¹⁰.

Metabolism

In vitro studies in human liver microsomes show that trazodone is metabolized to an active metabolite, m-chlorophenylpiperazine (mCPP) by cytochrome P450 3A4 (CYP3A4). This agent has high affinity for a number of serotonin receptors, including 5HT_{2C}>5HT₃>5HT_{2A}>5HT_{1B}>5HT_{1A}>5HT_{1D}, where it functions mostly as an agonist, in contrast to trazodone which acts as an antagonist at 5-HT_{2A} and 5-HT_{2C} receptors¹¹. The pharmacologic actions of mCPP may contribute to the net pharmacologic effects of trazodone, and could theoretically mitigate trazodone's direct antagonist actions at 5-HT_{2A} and 5-HT_{2C} receptors. However, plasma and brain levels of mCPP appear to be less than 10% of those of trazodone itself¹². Thus, the antagonist actions of trazodone are likely to overwhelm any effects of mCPP and block any agonist actions that mCPP may have at 5HT_{2A} and 5-HT_{2C} receptors. Other metabolic pathways that may be involved in metabolism of trazodone have not been well characterized.

Elimination

Approximately 60-70% of ¹⁴C-labelled trazodone hydrochloride was found to be excreted in the urine within two days and 9-29% in feces over 60-100 hours⁹.

Drug-drug interactions

In vitro drug metabolism studies reveal that trazodone is a substrate of the cytochrome P450-3A4 enzyme¹. Drug interactions have been reported with cytochrome P450-3A4 enzyme inhibitors, such as erythromycin, ketoconazole and ritonavir, leading to increased plasma concentration of trazodone. Conversely, carbamazepine may reduce trazodone plasma concentrations. Concurrent administration with other antidepressant drugs such as TCAs, monoamine oxidase inhibitors (MAOIs) or fluoxetine should be avoided due to the risk of developing serotonin syndrome and cardiovascular adverse effects. However, the benefits of a concomitant administration with a TCA or SSRI may outweigh the potential risks. For instance, the interaction between trazodone, citalopram and fluoxetine was studied in 97 patients with depressive syndrome over a 1-year period¹³. Results showed that the use of citalopram and fluoxetine in combination with trazodone had no significant impact on trazodone serum concentrations and no cases of headache, daytime sedation, fatigue or serotonin syndrome were reported during the study. The effect of short-term administration of ritonavir (200 mg twice daily, 4 doses) on the pharmacokinetics of a single dose of trazodone (50 mg) has been studied in 10

healthy subjects. The peak serum concentration (C_{max}) of trazodone increased by 34%, the area under the plasma drug concentration-time curve (AUC) increased 2.4-fold, the half-life increased by 2.2-fold, and the clearance decreased by 52%. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazodone were co-administered. Carbamazepine induces CYP3A4. Following co-administration of carbamazepine 400 mg/day with trazodone 100 mg to 300 mg daily, carbamazepine reduced plasma concentrations of trazodone by 76% and 60%, respectively, compared to pre-carbamazepine values¹⁴. This should theoretically lead to an increase in concentrations of mCPP.

Use in patients with renal or liver impairment

The effects of trazodone in patients with renal or hepatic impairment have not been well studied. Trazodone is extensively metabolized in the liver, so caution is needed with patients with hepatic impairment. Also, a case of severe liver toxicity resulting in fulminant hepatic failure has been reported following treatment with venlafaxine and trazodone for 4 months. The effects of 12 days' treatment with trazodone (75 mg/day) was evaluated in patients with mixed neuroses and normal or impaired renal function. Although higher serum concentrations of trazodone were observed in patients with renal impairment, compared to those with normal renal function, these differences were not statistically significant. As a result, the authors concluded that renal impairment is not a contraindication of treatment with low-dose trazodone. Given the available data on the use of trazodone in patients with renal or hepatic impairment, trazodone product labelling advises careful dosing and regular monitoring in patients with hepatic impairment, particularly in cases of severe hepatic impairment, and severe renal impairment. Usually, no dosage adjustment is necessary for mild to moderate renal impairment).

Clinical efficacy data

Efficacy and tolerability of trazodone in MDD

In several clinical studies, trazodone has proven comparable antidepressant often to other drug classes, such as tricyclic antidepressants (TCAs), SSRIs and SNRIs¹⁵. However, trazodone is sometimes used as a sedative-hypnotic rather than as a primary antidepressant, i.e. it is mainly prescribed in combination with other antidepressants, to target symptoms (e.g., insomnia) that are more likely to respond to trazodone than to the majority of the other antidepressants. The development of the prolonged-release, once-a-day formulation of trazodone, with the aim to optimize its antidepressant efficacy, and improve the treatment schedule and adherence in MDD patients, is gradually changing clinical practice and taking more advantage from trazodone multifunctional pharmacology and clinical efficacy in patients with MDD. In fact, the newer once-a-day formulation permits to start the medication at a dose (150 mg) which is already in the antidepressant range, this helping to more quickly achieve a full antidepressant effect. A summary of randomized, controlled clin-

ical trials of trazodone in adults with major depressive disorder published from 1981 to 2012 is reported in the first table of the reference Fagiolini et al.¹. The most significant trials, including those that have been published after 2012, are described below.

Trazodone versus TCAs

In short term (4-6 weeks) trials conducted in the 1980s, trazodone (prescribed at 100-400 mg/daily) resulted as efficacious as TCAs such as imipramine and amitriptyline¹⁶⁻¹⁸.

A double-blind, 4-week, placebo-controlled, randomized trial of elderly individuals with major depressive disorder, showed that trazodone was better than placebo and comparable to imipramine¹⁸.

Similarly, another randomized, double-blind trial in geriatric patients with major depressive disorder reported significant and comparable improvements in the total Hamilton Rating Scale for Depression (HAM-D) and Geriatric Depression Scale (GDS) scores for trazodone, amitriptyline and mianserin¹⁶.

Moreover, another in a study of geriatric patients with depression showed comparable improvement in HAM-D and Visual Analogue Scale (VAS) scores between trazodone and amitriptyline¹⁷.

A double-blind randomized trial compared trazodone (n=112), amitriptyline (n=44), mianserin (n=36), and dothiepin (n=35) finding no significant differences in improvement in depression between treatment groups¹⁹.

Another double-blind randomized small trial compared trazodone and amitriptyline showing no difference between the two medications in terms onset of antidepressant or anxiolytic activity²⁰.

A single blind study compared the effectiveness of intravenous trazodone and clomipramine, followed by oral administration of the same compound. Both i.v. trazodone and clomipramine resulted rapid and effective options for improving depressive symptoms and trazodone was better tolerated than clomipramine²¹.

Trazodone versus second-generation antidepressants (SGA)

Trazodone (dose range 150-450 mg) and second-generation antidepressants have been compared in several trials involving individuals with MDD.

A relatively large (n=126), head-to-head, double-blind, randomized trial comparing trazodone immediate release at 50-400 mg/day and fluoxetine at 20-40 mg/day, in patients with MDD, found comparable improvements for both medications. Not surprisingly, the study showed that HAM-D sleep disturbance scores improved significantly more in patients receiving trazodone than in patients receiving fluoxetine²². A smaller (n=27) 6-week study, compared trazodone and fluoxetine in elderly depressed patients and reported similar HAM-D score improvement for both medications²³. Two larger randomized, double-blind trials compared trazodone prolonged-release with paroxetine²⁴ and sertraline²⁵ respectively, in patients with MDD. Trazodone prolonged-release resulted as effective as paroxetine and sertraline in reducing depressive symptoms, as measured with HAM-D and

Montgomery Asberg Depression Rating (MADRS) scales. Moreover, trazodone showed advantages for patients with concomitant sleep disturbances.

A double-blind, placebo-controlled, randomized trial of 225 individuals with MDD tested the efficacy of trazodone immediate release (dose range 150-400 mg/day, after titration) and venlafaxine against placebo²⁶. Both trazodone and venlafaxine resulted significantly better than placebo in terms of changes in HAM-D scores. Compared to venlafaxine, trazodone showed a greater improvement in sleep disturbances than venlafaxine, whereas venlafaxine resulted better in terms of improving cognitive disturbance and retardation. A randomized, 6-week, double-blind study of mirtazapine and trazodone in a group of patients with moderate-to-severe MDD found a greater improvement in HAM-D scores for mirtazapine, compared with trazodone²⁷. However, a similar double-blind, 6-week, randomized study, again involving individuals with moderate-to-severe MDD, found no differences in HAM-D and Clinical Global Impression-Severity (CGI-S) scores between trazodone and bupropion, a dopamine and noradrenaline reuptake inhibitor²⁸. Interestingly, trazodone patients showed significantly greater improvements in HAM-D and CGI-S scores on day 7, compared to bupropion patients, due to trazodone beneficial effects on sleep.

Trazodone prolonged-release formulations

Trazodone delayed-release formulation and trazodone IR were compared in a double-blind, randomized study of 347 patients with MDD²⁹. Significant improvements from baseline in global severity, global improvement and HAM-D scores were seen for both treatment groups, after 6 weeks of treatment, with 150 mg/day given at bedtime. Small treatment differences in efficacy measures favored patients who received trazodone prolonged release but did not reach statistical significance. Safety, tolerability and adherence did not differ significantly between the two treatment arms, demonstrating that the newer delayed-release formulation was as safe and well tolerated as the IR formulation.

A double-blind, randomized, placebo-controlled study tested the efficacy and safety of trazodone extended release-contramid formulation (Tz-XR-COAD)³⁰. The study involved 412 patients with MDD treated for 6 weeks with Tz-XR-COAD at 150-375 mg/day. The mean maximum daily dose of Tz-XR-COAD administered during the study was 310 mg. The improvement in HAM-D scores were significantly greater with Tz-XR-COAD than with placebo, with a statistically significant difference that was already detected after the first week of treatment and then maintained throughout the study. Also, Tz-XR-COAD showed a higher percentage of HAM-D responders and a greater decrease in the change from baseline in the HAM-D depressed-mood item, CGI-S and MADRS total score. HAM-D items with the greatest improvement were: insomnia, feelings of guilt and depressed mood. MADRS items with the greatest improvement were: reduced sleep, inner tension, reported sadness and suicidal thoughts. Of interest, the antidepressant efficacy of Tz-XR-COAD was independent of the baseline severity of insomnia and of the improvement in insomnia. Tz-XR-COAD was well tolerated and the most frequent adverse events were headache and somnolence, which tended

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to subside over time. No serious treatment-related adverse events or clinically significant ECG or laboratory abnormalities were observed during the trial³⁰.

Češková et al.³¹ evaluated the efficacy, tolerability, and safety of Tz-XR-COAD in 85 patients with moderate to severe depression and reported a significant decrease in the overall MADRS and CGI score, noting that most patients reported improvement after 6 days of trazodone treatment. The most frequent adverse drug reactions (ADRs) were somnolence and fatigue. The authors concluded that Tz-XR-COAD had 'very good effects in clinical practice, both in previously untreated depressive episodes and in episodes not responsive to previous antidepressive therapy'.

Systematic review and network meta-analysis

Cipriani et al.³² conducted a systematic review and network meta-analysis for published and unpublished, double-blind, randomised controlled trials involving antidepressants. In head-to-head studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (range of ORs 1.19-1.96), whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were the least efficacious drugs (0.51-0.84). The lower efficacy that was recorded of trazodone may be due to several reasons, including relatively low sample size/number of studies analyzed and inability to investigate potentially important demographical and clinical variables able to affect treatment response at the individual patient level (e.g., age, sex, severity of symptoms, duration of illness, subtype of depression). In our experience, trazodone performs very well in patients experiencing depressive episodes with concomitant insomnia, anxiety or agitation, whereas it is not as good in patients with psychomotor retardation and hypersomnia.

INDICATIONS AND CLINICAL USE

TRAZODONE FORMULATIONS

Trazodone immediate release tablets

Indications

Trazodone IR indicated for the treatment of major depressive disorder (MDD) in adults^{3,6,9}.

Dosage and administration

Trazodone IR tablets may be divided in two or three parts. The initial dose in adults should be 75-150 mg/day, in divided doses. The dose may be then increased up to 300 mg/day, in divided doses, the largest of which should be taken at night. The dose may be increased up to 600 mg in hospitalized patients

Clinical practice

The dosage should be initiated at a low-dose and increased gradually, adjusting the dose as clinical response and

tolerability. Occurrence of sedation suggests the administration at bedtime of the major portion of the daily dose or a reduction of dosage.

The elimination half-life of trazodone IR is relatively short (6.6 h after a single 100-mg dose), therefore, repeated daily administrations are used to achieve a sufficient blood level for MDD patients, while decreasing the risk of side effects.

Trazodone immediate release liquid formulation (drops)

Indications

Trazodone IR liquid formulation is indicated for the treatment of depressive disorder, with and without anxiety component, in adults.

Dosage

In the 60 mg/ml formulation, 1 drop contains 2 mg of trazodone. In the older 25 mg/ml formulation, 1 drop contained 1 mg of trazodone. However, this formulation is no longer available. In the 60 mg/ml liquid formulation, 13-25 drops (26-50 mg), diluted in water or other beverage, should be given 2-3 times a day, when possible after a meal.

The dose may then be increased up to 300 mg/day, in divided administrations.

In hospitalized patients, the dose may be further increased up to 600 mg/day.

In elderly patients, the initial recommended dose is 100 mg/daily, in divided doses or in one single dose to be given at night. The dose may be increased as necessary (up to 300 mg/day), provided that the medication is administered in divided doses, avoiding to administer more than 100 mg at a time. In our practice (A. Fagiolini, personal communication), the initial dose in elderly patients, is often lower than 100 mg.

Clinical practice

In elderly patients, the possibility to start at a dose lower than the recommended dose of 100 mg/day is often considered. Depending on tolerability, the dose may then be increased as appropriate.

In adult patients, it is often helpful to start the medication at 25-50 mg administered at night, and then to gradually increase the dose, up to 75-100 mg at bedtime. Thereafter, the patient may add trazodone IR during the day, up to the desired – most effective target dose, based on the efficacy/tolerability ratio.

Trazodone injectable solution

Indications

Trazodone Injectable Solution is indicated for the treatment of depressive disorders, with and without an anxiety

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compared with the conventional IR formulation. Tz-XR-COAD is available in two strengths (150- and 300-mg scored tablets). The medication should be administered on an empty stomach to avoid a faster release of trazodone.

The incidence of treatment emergent adverse events reported by >10% of participants in the Tz-XR-COAD clinical trial mentioned above included headache (33% for Tz-XR-COAD patients vs 27% for placebo patients), somnolence (31% vs 16%), dry mouth (25% vs 13%), sedation (17% vs 3%), Fatigue (15% vs 8%), diarrhea (9% vs 11%).

Droup outs due to adverse events were 12% (25 of 202) in the Tz-XR-COAD group and 3% (6 of 204) in the placebo group.

Somnolence (31% Tz-XR-COAD vs 16% placebo), sedation (17% vs 3%) and fatigue (15% vs 8%) were more frequent in the Tz-XR-COAD than in the placebo group. However, many of these side effects tended to subside after a few days. The median duration of somnolence was 9 days in the trazodone group vs 4.5 days in the placebo group, the median duration of sedation was 12.5 vs 18 days, the median duration of fatigue was 23 days vs 19 days³⁰.

The main advantages of Tz-XR-COAD include³³:

- possibility to start the treatment at a dose which can well be already effective on depression, along with insomnia;
- low side effects risk (reduced blood peaks);
- 1 single administration in the evening, with blood peaks reduced.

COMBINED AND SEQUENTIAL TREATMENT WITH TRAZODONE

Combined antidepressant treatment

Owing to its 5HT_{2A} and 5HT_{2C} receptor antagonistic actions, trazodone has proven effective to prevent the occurrence of initial and long-term side effects of SSRIs, such as anxiety, insomnia and sexual dysfunctions^{34,35}. A synergistic antidepressant action is likely as well³⁶.

Also, trazodone adds to an SSRI treatment the benefits of its action on insomnia^{1,37}. To this end, trazodone may be helpful as a treatment for residual symptoms of depressive episodes which are not completely treated by another antidepressants, such as insomnia or anxiety.

Sequential treatment from parenteral trazodone to oral formulations

Intravenous-intramuscular trazodone is indicated for the treatment of depressive disorders, with and without an anxiety component. It is also indicated as an adjunctive medication for pain treatment and anesthesia. In our experience (A. Fagiolini, personal communication), this formulation is particularly useful in patients with depression and psychomotor agitation or depression and severe anxiety. Ballerio et al.³⁸ evaluated the effectiveness and safety of parenteral trazodone in 64 inpatients with bipolar depression and psychomotor agitation and observed significant improvements in CGI-S scores, with a good tolerability.

Fiorentini et al.³⁹ evaluated the efficacy of the sequential administration of trazodone i.v. for a week, followed by oral

+ i.v. trazodone, and then by oral trazodone alone. The study showed a favorable efficacy on depressive and anxiety symptoms, along with an acceptable tolerability profile.

TRAZODONE IN SPECIAL PATIENT POPULATIONS

Trazodone has been studied in several patient populations, including the elderly, the young and the individuals with renal impairment¹.

Pregnancy

In studies in rats, trazodone has been shown to cause increased fetal resorption and other adverse fetal effects when given at dose levels approximately 6 to 9 times the maximum recommended human dose. In rabbit studies, there was also an increase in congenital anomalies, at approximately 6 to 17 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. Hence, trazodone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

Trazodone and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when trazodone is administered to a nursing woman^{3,6,9}.

Children and adolescents

To date, there are no data on the use of trazodone in children and adolescents with MDD. In a small open-label study of ten children with chronic tic and Tourette's syndrome, the combination of haloperidol and trazodone was shown to improve clinical symptoms effectively. At study end, the Yale Global Tic Severity Scale score was significantly reduced from baseline, and no adverse effects were reported⁴⁰. However, it should be noted that trazodone is not recommended in children below the age of 18 years.

Elderly individuals

Reported clinical literature and experience with trazodone has not identified differences in responses between elderly and younger patients^{3,6,9}. However, as experience in the elderly with trazodone hydrochloride is limited, it should be used with caution in geriatric patients.

In late life individuals with MDD, comparable efficacy has been reported between trazodone and the TCA amitriptyline. Two double-blind, randomized studies comparing trazodone and fluoxetine also reported similar antidepressant efficacy between the two medications. Of interest, fluoxetine was associated with a higher incidence of activating adverse effects (agitation, anxiety, nervousness, insomnia), compared with trazodone. In contrast, sedating ef-

fects were more commonly reported with trazodone therapy versus fluoxetine.

Trazodone prolonged-release was evaluated in elderly patients with depression. After 4 weeks of treatment, both controlled-release and conventional formulations of trazodone (both given at night-time as single daily doses starting at 100 mg and increased to 200 mg/day based on tolerability) were similar in efficacy, as measured by changes from baseline in HAM-D and global assessments of the severity of depression scale scores. Fewer adverse effects were reported during the first week of treatment in patients receiving the controlled-release formulation^{3,6,9}.

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction.

OTHER CLINICAL USES

Trazodone is indicated for MDD. However, many patients with MDD present with comorbid symptoms, conditions and diseases, such as anxiety, post-traumatic stress disorder (PTSD), bulimia, fibromyalgia, insomnia, sexual dysfunction, neurocognitive disorders, substance/alcohol use disorders, and akathisia. To this end, we decided to review the efficacy of trazodone as an aid for patients with the above comorbidities.

Anxiety and PTSD

Trazodone has proven useful in the treatment of generalized anxiety disorder⁴¹, with an efficacy comparable to that of imipramine and diazepam⁴².

In panic disorder, the usefulness of trazodone is yet to be established. Studies have been published in which the medication did not seem particularly beneficial⁴³, whereas other studies showed significant improvements in several clinical manifestations of panic disorder, as well as on generalized anxiety, phobias, depression and avoidance conduct⁴⁴.

In PTSD, trazodone is usually considered a second line medication, when SSRIs have failed⁴⁵.

For instance, patients with PTSD, trazodone has demonstrated a significant improvement in social and occupational functioning⁴⁶. A high prevalence (70-91%) of sleep disturbances has been demonstrated in patients with PTSD, with special reference to difficulty falling and staying asleep and trazodone may be particularly useful in these situations. For instance, in a survey testing the usefulness of trazodone for insomnia and nightmares in patients with PTSD⁴⁷, 72% of the 60 participating individuals reported a decrease in the number and intensity of nightmares, 92% found less difficulty falling sleep and 78% showed improvements in sleep continuity.

Bulimia

In a 6-week, double-blind, placebo-controlled trial in 42 women with bulimia nervosa, trazodone was significantly superior to placebo in reducing the frequency of episodes of binge eating and vomiting. The medication was well tolerated. Also, the longer-term follow-up demonstrated that 72% of patients continued to improve over time⁴⁸.

Trazodone efficacy for bulimia was also studied in a small open-label, flexible-dose study at a mean dose of 410 mg (range, 250-600 mg). The number of binge eating and vomiting episodes was significantly decreased. Carbohydrate cravings and urges to binge eat were significantly diminished in intensity as well⁴⁹.

Fibromyalgia

In an open-label 12 week study involving patients with fibromyalgia, Trazodone improved sleep quality and showed a significant efficacy on other fibromyalgia symptoms, as measured by Fibromyalgia Impact Questionnaire⁵⁰.

A 24-week, open-label study of 66 patients with fibromyalgia, trazodone (50-300 mg/day) significantly improved global fibromyalgia severity, depression, sleep quality, and pain interference with daily activities. After pregabalin (75-450 mg/day) combination additional and significant improvements were seen on pain interference with daily activities, fibromyalgia severity, and depression. Of interest, combined treatment also showed a significant decrease in bodily pain and only two patients dropped out due to side effects during the second, combination phase, of the study⁵¹.

Insomnia

Trazodone is generally considered as a valuable tool for the treatment of insomnia. In 2004, trazodone was reported as the most commonly used hypnotics in the United States⁵².

Several studies have reported on the hypnotic effect of trazodone, both in patients suffering from primary insomnia and in patients suffering of insomnia as a symptom of a major depressive disorder. Also, the efficacy of trazodone in the treatment of insomnia has been shown in patients with dementia, anxiety disorders and post-traumatic stress disorder^{47,53}. Most trials have reported on a favorable hypnotic effect of trazodone in depressed patients treated with other antidepressants³⁷.

Trazodone was compared to quetiapine among psychiatric patients. The study outcomes measures included sleep time, number of night-time awakenings, sleep efficiency, sleep latency, length of hospitalization, and patient-reported side effects. The results showed that, with respect to total sleep time and night-time awakenings, trazodone was more effective than quetiapine⁵⁴.

A recent observational study suggested that trazodone may be an effective drug for the treatment of insomnia and nightmares in patients with advanced cancer⁵⁵. However, trazodone failed to show a significant improvement in subjective or objective sleep in methadone-maintained persons with sleep disturbance⁵⁶.

Of interest, a few case reports have suggested the efficacy of trazodone for sleep disorders such as narcolepsy and cataplexy⁵⁷.

A recent systematic review⁵⁸ pointed that trazodone has repeatedly demonstrated effective for primary insomnia, as well as secondary insomnia, including the insomnia symptoms associated with depression and dementia. The authors concluded that there are adequate data supporting the efficacy and general safety of the low-dose use of trazodone for

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the treatment of insomnia. A summary of several trazodone clinical trials reporting sleep endpoints is reported in Fagiolini et al.¹, table 2.

Neurocognitive disorders

A large number of patients with dementia develop behavioral and psychiatric conditions, which often include symptoms of depression, such as depressed mood, agitation, insomnia, lack of interest, lack of motivation, and changes in appetite

Indeed, it is estimated that up to 80% of patients with dementia develop behavioral and psychiatric conditions during the course of their disease⁵⁹. Those symptoms increase the burden on the caregivers, decrease quality of life for patients, and increase the likelihood of admission to an institution.

In a recent study in mouse models of neurodegeneration⁶⁰, demonstrated that trazodone, used at clinically relevant doses over a prolonged period of time, resulted markedly neuroprotective, without systemic toxicity. Specifically, in tauopathy-frontotemporal dementia mice, trazodone resulted neuroprotective, reduced hippocampal atrophy, rescued memory deficits and reduced p-tau burden. In prion-diseased mice, trazodone restored memory deficits, stopped the development of neurological signs, prevented further neurodegeneration and significantly prolonged survival.

In a retrospective study of the medical records of a small number of patients with Alzheimer Disease, an improvement of psychiatric symptoms was seen after trazodone in 75% of patients⁶¹.

In another study, 22 patients with dementia and behavioral problems were treated with trazodone at a mean daily dose of 172±107 mg and showed an improvement in several psychometric scales, including the HRS. Of interest, 82% of the patients showed moderate-to-marked improvement, with most patients who were able to return to their preadmission residence. Trazodone was generally well tolerated except for occasional sedation effects⁶².

A randomized, placebo-controlled, double-blind, crossover study, evaluated the effect of trazodone on behavioral problems in patients with frontotemporal dementia and showed a significant decrease in the Neuropsychiatry Inventory total score with trazodone. Of interest, this improvement was mainly based on 4 items of the scale: irritability, agitation, depressive symptoms and eating disorders⁶³.

A randomized, double-blind, parallel-group, 9-week treatment trial was conducted in patients with dementia and agitated or aggressive behaviors, who were treated with either haloperidol 1 to 5 mg/day or trazodone 50 to 250 mg/day. The results showed that depressive symptoms and agitated behavior were associated with greater behavioral improvement in patients treated with trazodone. Of interest, repetitive, verbally aggressive, and oppositional behaviors responded preferentially to trazodone, whereas symptoms of excessive motor activity and unwarranted accusations responded preferentially to haloperidol^{64,65}.

An open label, observational and review study evaluated the use of trazodone in 68 elderly patients with Alzheimer's disease and other dementias, clinically presenting with sleep problems and treated with hypnotic medications. Trazodone was the most commonly used drug among patients (n=5),

with an effectiveness of 65.7%⁵³. As in the previous trial, however, the patients were not specifically recruited based on the presence of depression.

Sexual dysfunction

Studies of trazodone for sexual dysfunction have led to mixed results. In fact, some studies showed that trazodone did not differentiate from placebo in improving erections and sexual function but other studies indicated trazodone efficacy for sexual dysfunctions, including SSRI-induced sexual dysfunctions³⁷. This may be explained by the fact that trazodone inhibits serotonin transport and, at the same time, inhibits 5-HT_{2A} and 5-HT_{2C} receptors, which leads to an antidepressant action without sexual disorders^{1,37}.

A recent study⁶⁶ systematically evaluated the literature to evaluate the efficacy of trazodone for the treatment of hypoactive sexual desire disorder (HSDD). Interestingly according to receptor and pharmacokinetics (PK) data the author estimated that 4-20 mg extended-release (XR-COAD) trazodone daily (bioequivalent to 1.2-6.4 mg immediate-release trazodone 3 times a day) were the minimum effective dose for improving sexual desire and arousal; whereas 75 mg (25 mg immediate-release, three times a day) resulted instead to be the threshold dose for depression. The author concluded that HSDD or arousal problems might be treated without over-sedation with a quarter (37.5 mg) of a 150-mg XR-COAD trazodone tablet or 50-mg IR trazodone tablet quartered to 12.5 mg given 2-3 times daily or as needed for arousal problems. They cautioned that interindividual sensitivity might require varying the dose.

Substance/alcohol use disorders

The effects of an oral 2-mg/kg dose of cocaine hydrochloride were measured in eight cocaine-using men after pretreatment with a single, 100-mg oral dose of trazodone or placebo, in a double-blind study. Trazodone pretreatment reduced the cocaine-induced effects of increased blood pressure, decreased skin temperature, and increased pupil size. Trazodone did not alter plasma epinephrine or norepinephrine levels. Feelings of tension and shakiness after cocaine administration were diminished as well⁶⁷. Cocaine use is often associated with the development of a foraging, i.e. a compulsive behavior consisting in searching for pieces of crack cocaine that the individual believes might have been accidentally misplaced. In three patients with a long history of abusing crack cocaine, the use of trazodone led to remission of cocaine-induced compulsive foraging behavior and resulted in the prevention of relapse into cocaine use⁶⁸.

Trazodone has proven effective to treat insomnia during alcohol withdrawal, with lower than benzodiazepines of drug to drug interaction and cross tolerance with alcohol^{1,69-72}.

Trazodone was tested against placebo for the ability to increase sleep efficiency in alcohol-dependent patients after detoxification. Sixteen patients received trazodone (n=8) or placebo (n=8) and polysomnography was performed at baseline, after the 1st dose, and after 4 weeks of treatment. Secondary outcomes included changes in other sleep parameters, HAM-D, Clinical Global Impression (CGI) scales. Tra-

zodone increased sleep efficiency at all 3 study time points. Sleep improvement in trazodone patients included the number of awakenings, intermittent wake sleep time, and non-rapid eye movement sleep. HAM-D and CGI scores were better in trazodone group than placebo⁷⁰. Animal studies have suggested the possibility that trazodone is able to decrease opioid withdrawal⁷³.

Trazodone has also been studied as a means to decrease withdrawal symptoms from benzodiazepines. Ten benzodiazepine-dependent patients were treated with trazodone (100 mg three times a day) while their benzodiazepines were progressively tapered and then followed up at monthly intervals. Withdrawal symptoms were very limited and all patients remained off benzodiazepines and showed no evidence of abuse of trazodone during the entire 1 year follow up period. Ratings of anxiety and depressive symptoms significantly improved during follow-up: from 12.3 to 5.4 on the Hamilton Rating Scale for Anxiety and from 11.6 to 4.8 on the HAM-D⁷⁴.

Antipsychotic-induced akathisia

Antipsychotic-induced akathisia (psychomotor restlessness) is a common drug-induced movement disorder that may require active treatment as the offending drug often cannot be reduced or withdrawn⁷⁵. There is emerging evidence that trazodone may be a useful addition to the currently available pharmacopoeia.

A preliminary pilot trial tested the efficacy of trazodone, titrated within 5 days up to 100 mg/die in the treatment of antipsychotic-induced akathisia in 9 patients, yielding positive results⁷⁶. A subsequent controlled cross-over study with placebo in 13 patients by the same authors has confirmed findings of efficacy⁷⁷. An independent case report of a risperidone-induced akathisia suggests the efficacy of trazodone in conditions resistant to conventional treatment, i.e. propranolol, biperiden and clonazepam⁷⁸. This admittedly limited evidence of efficacy is consistent with, and strongly reinforced by theoretical considerations on the role of increased serotonergic transmission in the pathogenesis of SSRI-induced akathisia and more importantly by findings of efficacy reported by a number of controlled trials in the treatment of antipsychotic-induced akathisia with other 5HT_{2A/C} antagonists, like mianserin and mirtazapine⁷⁹.

TOLERABILITY OF TRAZODONE

Trazodone is usually well tolerated for the treatment of MDD, with the most common adverse effects being somnolence/sedation, headache, dizziness and dry mouth^{3,6,9}.

Sedation and orthostatic hypotension

Drowsiness is the most common adverse effect of trazodone, with a reported incidence in depressed patients ranging from 5.6 % to 41 %. An increased risk of orthostatic hypotension may be seen, particularly in elderly patients or those with pre-existing heart disease. This effect, due to adrenergic alpha 1-receptor blockade, is often transient and related to plasma drug concentration^{3,6,9}.

Arrhythmias

At toxic plasma concentrations, trazodone may be associated with prolongation of the corrected QT interval (QTc) and torsade de pointes. Even with therapeutic doses, cases of life-threatening cardiac arrhythmias, including ventricular tachycardia have been reported in clinical and preclinical studies. The prolongation of QT interval may be related to the interaction of trazodone with hERG potassium channels¹. 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^{3,6,9}.

Priapism

Trazodone may be associated with rare occurrences of priapism. Hence, the medication 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)¹. Patients taking trazodone should be advised to refer to an emergency room in case of priapism.

Serotonin syndrome

The concomitant use of trazodone with other drugs that potentiate serotonin, such as SSRIs, SNRIs, triptans, tricyclic antidepressants, lithium, tryptophan, tramadol, buspirone, fentanyl, amphetamines, St. John's Wort, and with drugs that alter the metabolism of serotonin (such as, monoamine oxidase inhibitors, MAOIs) may increase the risk of serotonin syndrome^{3,6,9}. Symptoms of serotonin syndrome include agitation or restlessness, confusion and mental status changes (e.g., agitation, hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea), tachycardia, hypertension, dilated pupils, loss of muscle coordination or twitching muscles, muscle rigidity, sweating, diarrhea, headache, shivering, piloerection, fever, seizures, arrhythmia, loss of consciousness. In our clinical experience, we have not observed any case of serotonin syndrome with the combination of trazodone with SSRIs, lithium, triptans, tricyclic antidepressants. However, the combination with certain medications, including but not limited to MAOIs, should be avoided and patients should be carefully evaluated when taking trazodone in combination with other serotonergic medications, especially if/when trazodone is prescribed at higher doses. Trazodone should not be used in combination with an MAOI or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping trazodone before starting an MAOI.

Activation of mania/hypomania

Patients and their caregivers should be advised to observe for signs of activation of mania/hypomania and instructed to report those symptoms to the healthcare provider^{3,6,9}.

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Increased risk of bleeding

As for many other antidepressants, the concomitant use of trazodone hydrochloride tablets with aspirin, NSAIDs, other antiplatelet drugs, warfarin, or other anticoagulants may increase the risk of bleeding, because of the interference with serotonin reuptake^{3,6,9}.

Orthostatic hypotension and syncope

Hypotension, including orthostatic hypotension and syncope has been reported in patients receiving trazodone hydrochloride. Concomitant use of trazodone with an antihypertensive medication may require a reduction in the dose of the antihypertensive.

Hyponatremia

Hyponatremia with antidepressants is often the result of a SIADH (syndrome of inappropriate antidiuretic hormone secretion). Cases with serum sodium lower than 110 mmol/L have been reported in patients taking trazodone. Elderly patients or patients taking diuretics may be at greater risk of developing hyponatremia with antidepressants. Symptoms of hyponatremia include headache, reduced concentration, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. More severe and/or acute cases may present with hallucination, syncope, seizure, coma, respiratory arrest, and death^{3,6,9}.

Worsening of depression and suicidality risk

Cases of suicidal ideation and suicidal behaviors have been reported during trazodone therapy, or early after treatment discontinuation. In short-term studies of MDD and other psychiatric disorders in children, adolescents and young adults, antidepressants have increased the risk of suicidal thinking and behavior (suicidality) compared with placebo. As with other antidepressants, it is necessary to appropriately monitor and closely observe patients receiving trazodone for any reason, particularly during initiation of therapy (i.e. the first few days) and during periods of dosage adjustments.

Particular clinical attention is required for patients presenting with emerging suicidality or with a worsening of symptoms of anxiety, agitation, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, and/or mania, which are often present in patient at higher suicide risk.

Potential for cognitive and motor impairment

Trazodone may cause somnolence or sedation and may impair the mental and/or physical ability required for driving or for the performance of potentially hazardous tasks. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that the drug treatment does not affect them adversely^{3,6,9}.

Other adverse events

Other adverse events are described in the prescribing information^{3,6,9}.

CONCLUSIONS

Trazodone is an established antidepressant with a favorable efficacy profile for the treatment of depression. The appropriate antidepressant doses are usually 150-300 mg/day and are often higher than the doses used when trazodone is prescribed to augment the antidepressant effect of another medication (i.e. to address insomnia). Trazodone is usually well tolerated and has a low risk of anticholinergic side effects (such as constipation, urinary retention, dry mouth), of weight gain and of sexual side effects. Trazodone is particularly helpful in patients with depression and concomitant insomnia. Trazodone may also be helpful for patients with concomitant anxiety and, especially in its intravenous-intramuscular formulation, may be helpful in patients with concomitant agitation. Trazodone favorable effect on insomnia, and possibly on anxiety and agitation, may be seen also when trazodone is used to augment the effects of other antidepressants.

Conflicts of interests: Cuomo is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Lundbeck, Otsuka; Ballerini is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Lundbeck, Janssen, Otsuka; Bruni is/has been a consultant and/or a speaker and/or has received research grants from Biogen, Angelini; Decina is/has been a consultant and/or a speaker and/or has received research grants from Angelini; Di Sciascio is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Arcapharma, FB-Health, Italfarmaco, Janssen, Lundbeck, Otsuka, Polifarma, Recordati, Sanofi Aventis; Fiorentini is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Lundbeck, Janssen, Otsuka; Scaglione is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Astellas, Bayer, GSK, Janssen, Pierre Fabre, MSD, Sanofi Aventis, Vifor; Vampini is/has been is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Errekappa Euroterapici, GlaxoSmithKline, Janssen, Lundbeck, Otsuka, Sanofi Aventis; Fagiolini is/has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Apsen, Boehringer Ingelheim, Doc Generici, FB-Health, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer, Recordati, Sanofi Aventis, Sunovion, Vifor.

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