

Review

Trazodone: A Review of Its Pharmacological Properties and Its Off-Label Use in Dogs and Cats

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Abstract: Trazodone is approved by the Food and Drug Administration (FDA) for the treatment of depression and anxiety in humans, it can perform these functions due to its selective serotonin receptor antagonism and reuptake inhibition properties. Trazodone has not been approved for animals by the FDA but it is legally prescribed by veterinarians as an off-label drug for dogs and cats. This review describes trazodone's mechanism of action, pharmacokinetic properties and adverse effects and summarizes the benefits of trazodone for non-approved FDA indications to reduce anxiety, behavioral stress, sedation, pre-and post-operation stress. It also discusses its cardiac safety profile for dogs and cats. As few clinical trials have been conducted to evaluate trazodone's efficacy for treatment of the many behavioral and medical conditions in animals, large and randomized controlled clinical trials are still needed to confirm its efficacy in clinical practice.

Keywords: Clinical Practice, Efficacy, Off-Label

Introduction

Trazodone, a second-generation triazolopyridine derivative (Fig. 1), was approved in the '70s for the treatment of depression and still represents an effective therapeutic option for depressive disorders with or without an anxiety component. Beyond its antidepressant activity, trazodone was also found to be beneficial in the off-label treatment of medical and psychiatric conditions such as insomnia, anxiety, post-traumatic stress, obsessive compulsive and feeding and eating disorders, behavioral disturbances associated with cognitive dysfunction, sexual dysfunction, certain pain conditions and rehabilitation after acute ischemic stroke (Bossini *et al.*, 2012; Khouzam, 2017; Stahl, 2008). Trazodone selectively antagonizes serotonergic (5-HT_{2A} and 5-HT_{2C}) receptors and serotonin reuptake inhibition (Saletu-Zyhlarz *et al.*, 2003; Stahl, 2009). Trazodone is a moderately potent α -adrenoceptor and histaminergic (H₁) antagonist and possesses anxiolytic and hypnotic properties (Stahl, 2009). Despite the existence of this compound for nearly 40 years, its mechanism of action has not been fully clarified and continues to be the subject of research.

Mechanism of Action

The main pharmacological property of trazodone is its potent competitive binding to 5-HT_{2A} receptor antagonists. At a very low dose (1 mg) trazodone

occupies about half of the 5-HT_{2A} receptors (Stahl, 2009). At low to moderate doses (25-150 mg), trazodone mainly acts to antagonize postsynaptic 5-HT_{2A} receptors as well as histaminic (H₁) and adrenergic (α -1) receptors, which may account for some of its hypnotic effects. At higher doses (150-600 mg), trazodone also acts as an antagonist at postsynaptic 5-HT_{2A/2C} receptors as well as blocking the Serotonin Transporter (SERT) on the presynaptic neuron (Stahl, 2009). The latter dose range has been used to produce an antidepressant effect (Stahl, 2009). Trazodone's ability to block SERT is at least 100 times less potent than its ability to block the 5-HT_{2A} receptors (Stahl, 2009). The dual action of 5-HT_{2A} antagonism and SERT inhibition leads to positive clinical pharmacological results (Stahl, 2009).

In humans, trazodone is converted by Cytochrome (CYP) 3A4 into an active metabolite known as meta-chloro-phenyl piperazine (mCPP) (Fig. 1). This metabolite has high affinity for a number of serotonin receptors as 5-HT_{2C}>5-HT_{2A}. It acts as an agonist, whereas trazodone acts as an antagonist at 5-HT_{2A} and 5-HT_{2C} receptors. These pharmacologic actions of mCPP may contribute to the net effects of trazodone and could probably mitigate trazodone's antagonism on 5-HT_{2A} and 5-HT_{2C} receptors. Because plasma and brain levels of mCPP appear to be less than 10% of those of trazodone, as a result, the antagonist action of trazodone appears to overwhelm any effects of mCPP. In short, any antagonism that mCPP might have on 5-HT_{2A} and 5-

HT2C receptors seems to be negligible. However, possible interactions between mCPP and other drugs metabolized by CYP3A4 may modify trazodone's pharmacologic effects (Stahl, 2009).

Pharmacokinetic Studies

As trazodone is used for treating depression and anxiety disorders in humans, there are reports on the pharmacokinetics of trazodone in humans (Bayer *et al.*, 1983; Catanese and Lisciani, 1970; Greenblatt *et al.*, 1987; Jackson *et al.*, 1982; Mercolini *et al.*, 2008; Nilsen and Dale, 1992; Si *et al.*, 1991; Vatassery *et al.*, 1997). However, the pharmacokinetics of this drug has been sparsely documented in dogs (Catanese and Lisciani, 1970; Jay *et al.*, 2013), in rats (Catanese and Lisciani, 1970; DeVane *et al.*, 1999) and no reports are presented in other species, particularly in cats.

Two pharmacokinetics studies have been performed in dogs. The first kinetics study was performed in the '70s. This investigated the absorption and distribution of trazodone in a rat, dog and human models. It showed that trazodone was absorbed less in dogs compared to humans but more than in rats (Catanese and Lisciani, 1970). In that study, it was reported that C_{max} was $2.5 \mu\text{g mL}^{-1}$ and $4.8 \mu\text{g mL}^{-1}$ for dogs that received trazodone orally at a dose of 20 mg kg^{-1} and 50 mg kg^{-1} , respectively (Catanese and Lisciani, 1970).

Over 40 year later, another pharmacokinetic study was conducted in adult male dogs to observe the effects of trazodone administered at 8 mg kg^{-1} as a single dose both in intravenous (IV) and oral (PO) administrations. Results indicated that the PO administration was better tolerated in all dogs compared to the IV administration. Substantial adverse effects, tachycardia and behavior disinhibition, were noted with IV administration. The PO route resulted in acceptable absolute bioavailability (84.6%), although considerable variability in T_{max} was found (Jay *et al.*, 2013). Since adverse effects occurred after IV administration, a substantial reduction of the dose is recommended when the drug is used via parenteral routes (Jay *et al.*, 2013). Notably, the injectable solution of trazodone is not yet available for clinical practice.

A search for information on the pharmacokinetics of trazodone in cats was also attempted from different scientific data bases; however, no reports were found for this species. In contrast, two clinical studies of trazodone that reported sedative and anxiolytic properties in cats were found (Orlando *et al.*, 2016; Stevens *et al.*, 2016). Although there is a lack of trazodone studies in cats, trazodone has been documented to be administered at $1\text{-}2 \text{ mg kg}^{-1}$ in this animal species (Perrin *et al.*, 2014).

The active metabolite (mCPP) of trazodone has been studied in humans (Rotzinger *et al.*, 1998) and in rats (DeVane *et al.*, 1999). However, no data has been reported regarding this metabolite in dogs and cats yet. Further studies are needed to detail the pharmacokinetic pattern for this metabolite in these two animal species.

Fasting status has been reported to affect the PK of oral trazodone. Jay *et al.* (2013) reported that presence of food in the upper gastrointestinal tract may delay absorption of trazodone in dogs. Trazodone's C_{max} and T_{max} may be improved with fasting. Indeed, the C_{max} peak was within the range 2.5-7.5 h in fasting dogs (Catanese and Lisciani, 1970; Jay *et al.*, 2013). The T_{max} was shortened to 0.5 h when animals were fed 1 h prior to drug administration (Jay *et al.*, 2013). T_{max} was variable in individual animals as shown by Jay *et al.* (2013); 5 of 6 dogs had a T_{max} value between 8-10 h while 1 dog had a value of 0.5 h.

Pharmacokinetic parameters of trazodone have also been shown to vary with age and sex in humans (Bayer *et al.*, 1983; Greenblatt *et al.*, 1987). It has been reported that C_{max} and T_{max} were comparable in both young and elderly, but the area under the plasma concentration-time curve of the drug was significantly greater in the latter after a single oral dose of 100 mg trazodone (Bayer *et al.*, 1983). Other studies indicated that T_{max} and $T_{1/2}$ were greater in the elderly than in the young, as well as in women than men after 50 mg oral dose of trazodone in 43 healthy subjects (Greenblatt *et al.*, 1987). As few pharmacokinetic studies are reported in dogs, the pharmacokinetics of trazodone in these animals should be further investigated on the base of animal age, sex and breed.

Side Effects of Trazodone

The known adverse effects associated with oral administration of trazodone in dogs and cats are basically mild and well-tolerated. The most common adverse effects of oral trazodone include gagging, vomiting, colitis, sedation, increased appetite, paradoxical excitement and panting, hyper salivation and behavior disinhibition in dogs (Gilbert-Gregory *et al.*, 2016; Gruen and Sherman, 2008; Jay *et al.*, 2013) and sedation and behavior disinhibition (struggling, aggression and vocalization) in cats (Orlando *et al.*, 2016; Stevens *et al.*, 2016). Trazodone may not cause cardiovascular depression in dogs and cats after oral administration (Jay *et al.*, 2013; Orlando *et al.*, 2016) although some studies reported this adverse event in humans (Rausch *et al.*, 1984; Reeves and Bullen, 1995; Service and Waring, 2008). However, tachycardia was reported in experimental dogs immediately after IV administration at high trazodone blood concentrations (Jay *et al.*, 2013) and in anesthetized dogs when compared with imipramine at the same dose after IV administration (Gomoll *et al.*, 1979; Gomoll and Byrne, 1979; Je and Aw, 1982). Intraoperative hypertension and bradycardia developed in healthy dogs undergoing anesthesia for orthopedic surgery when compared with acepromazine (Murphy *et al.*, 2017). Other adverse events such as priapism (seldom reported in humans) was found in 1 out of 15 dogs that received trazodone 24 h after undergoing anesthesia for orthopedic surgery (Murphy *et al.*, 2017).

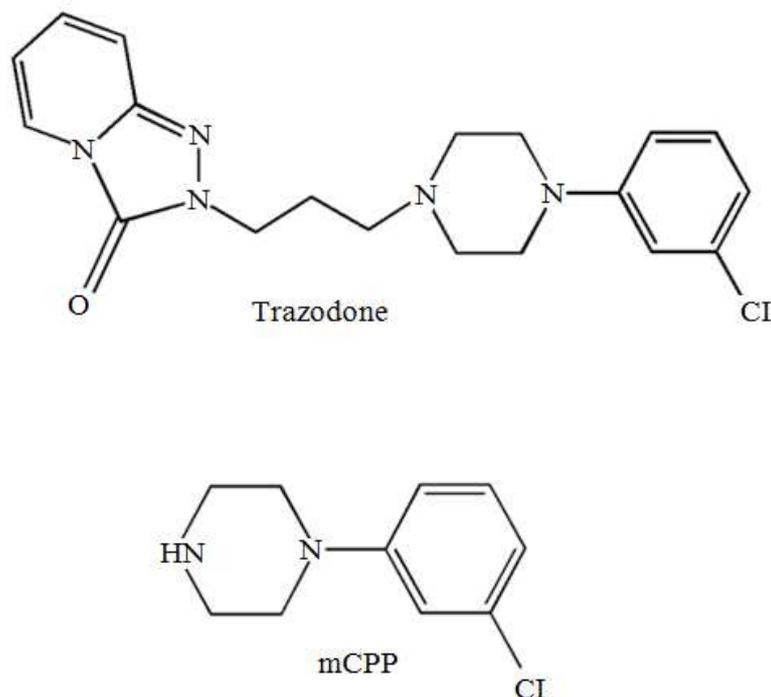


Fig. 1. Chemical structure of trazodone and mCPP

Trazodone is reported to have potential risk for the serotonin syndrome when used with other Selective Serotonin Reuptake Inhibitor (SSRI) and/or Tricyclic Antidepressant (TCA) agents. Although serotonin syndrome has not been described in animals after trazodone administration, it is likely that trazodone can be used as an adjunctive agent in combination with other behavioral drugs, TCA or SSRI, opioid drugs, and antimicrobials. Former studies reported that it was well tolerated over a wide dose range in dogs (Gilbert-Gregory *et al.*, 2016; Gruen *et al.*, 2014; Gruen and Sherman, 2008) and probably in cats as well. However, clinicians that are unfamiliar with combined use of serotonin enhancing medications are strongly recommended to ensure safety and efficacy of trazodone (Gilbert-Gregory *et al.*, 2016).

The safety profile of trazodone has been speculated to not be affected by breed, age, or dose in dogs (Gilbert-Gregory *et al.*, 2016; Gruen *et al.*, 2014; Gruen and Sherman, 2008) and cats (Orlando *et al.*, 2016; Stevens *et al.*, 2016). However there is no specific report to confirm and this issue should be further investigated. Most side effects resolve with time and monitoring is the best response to the appearance of mild to moderate side effects. For the dose regimen it is best to begin at the lower end of the dosage range to limit side effects. Indeed, administering a half dose for three days and then gradually tapering up as needed resulted in less side effects in dogs (Gruen and Sherman, 2008).

Trazodone Use for Anxiety

Due to extensive use of trazodone for treating depressive and anxiety disorders as well as medical and psychiatric conditions in humans, its off label use for the treatment of signs of anxiety in dogs and cats has recently gained popularity.

Canine and feline anxiety disorders such as travel, separation, noise phobia, veterinary visits and hospitalization are common but probably under-estimated. The first report on the use of trazodone for treating anxiety disorders including separation, storm, noise, inoculation and travel phobia, generalized anxiety and canine compulsive disorder in dogs showed that trazodone alone or in combination with other medications including tramadol, NSAIDs, antimicrobials and various behavior-modifying drugs induced a few adverse effects (gastrointestinal distress, behavioral changes, or sedation). It was tolerated over a wide dose range and calmed behavior in various breeds, sexes and ages of dogs (Gruen and Sherman, 2008). The daily medication ranged from 1.9-16.2 mg kg⁻¹ but should not exceed 300 to 600 mg/24 h. During a particular event (e.g. storm phobia) however, the daily dose can be cumulated as needed to a dose in the range 2.2 to 14.0 mg kg⁻¹ (Gruen and Sherman, 2008) (Table 1). Because this finding is extrapolated from a retrospective case series, further controlled studies of dose range, efficacy and safety are required to provide an additional therapeutic option for using trazodone in dogs that are unresponsive to conventional treatments (Gruen and Sherman, 2008).

Table 1. The doses of trazodone for various behavioral and medical conditions

Conditions	Dogs	Cats	References
Anxiety	- 1.9-16.5 mg kg ⁻¹ q 24 h (for daily medication) or 1.7-19.5 mg kg ⁻¹ q 24 h (combined daily [q 8-24 h] and as-needed administration) or 2.2-14 mg kg ⁻¹ q 24 h (as-needed administration) for general anxiety - 4-12 mg kg ⁻¹ q 24 h for 1.5 h prior to a veterinary visit	- 7.7-15.2 mg kg ⁻¹ q 24 h for 1-1.5 h prior to a veterinary visit	Gruen and Sherman (2008) Stevens <i>et al.</i> (2016) Herron and Shreyer (2014)
Behavioral stress	- 3-7 mg kg ⁻¹ alone or combine with NSAIDs, tramadol and other medications	- No published dose	Gilbert-Gregory <i>et al.</i> (2016)
Sedation	- 3-5 mg kg ⁻¹ q 12-24 h	- 10.6-16.7 mg kg ⁻¹ q 24 h for 50 mg tablet - 21.3-33.3 mg kg ⁻¹ q 24 h for 100 mg tablet	Orlando <i>et al.</i> (2016) Gruen and Sherman (2008)
Pre-operation	- 5-7 mg kg ⁻¹ given prior 2 h combines with opioid as premedication for anesthesia and orthopedic surgery	- No published dose	Murphy <i>et al.</i> (2017)
Post-operation	- 3.5 mg kg ⁻¹ combine with tramadol for 3 days and then 7 mg kg ⁻¹ q 12 h or 7-10 mg kg ⁻¹ q 8 h as-needed for 4-12 weeks for orthopedic surgery	- No published dose	Gruen <i>et al.</i> (2014)

The second study reported that trazodone has been recommended to promote low-stress veterinary visits for dogs (Herron and Shreyer, 2014) and cats (Stevens *et al.*, 2016) that have signs of anxiety. In dogs, trazodone (dose 4 to 12 mg kg⁻¹, not exceeding 300 mg per animal) administered by the owner 1.5 h prior to a veterinary visit significantly reduced stress associated with handling and examination (Herron and Shreyer, 2014). In cats, a dose between 7.7 and 15.2 mg kg⁻¹ of trazodone administered by the owner 1-1.5 h prior to a veterinary visit resulted in significantly fewer signs of transport- and examination-related anxiety compared to placebo as control. Trazodone was well tolerated by most cats in the double-blind randomized crossover study (Stevens *et al.*, 2016). Because of the low numbers of cats of various ages, few cats had one or more of the evaluated signs of anxiety or presence of adverse events (vocalization and agitation). Pharmacodynamic and pharmacokinetic studies should be performed to ensure the safety and efficacy of this drug for treatment of anxiety in cats (Stevens *et al.*, 2016).

Trazodone Use for Behavioral Signs of Stress

Hospitalized animals such as dogs specifically have signs of acute and chronic psychogenic stress resulting from invasive procedures, novel environments, confinement and separation from familiar individuals (Gilbert-Gregory *et al.*, 2016). Trazodone has been applied to treat behavioral signs of stress in dogs during hospitalization but no report has been investigated in cats. According to a recent study, trazodone in a dose range from 2.83 to 6.75 mg kg⁻¹ reduced stress-related signs and behaviors of hospitalized dogs when used alone or in combination with NSAIDs, tramadol and other medications without

any adverse events (Gilbert-Gregory *et al.*, 2016). Furthermore, trazodone reduced hospitalization time in dogs. Gilbert-Gregory *et al.* (2016) showed that dogs with signs of behavioral stress treated with trazodone were hospitalized for 1-4 days (mean 1.5±0.8 days) compared to the environmentally matched dogs that were hospitalized for 1-11 days (mean 2.0±2.0 days) (P = 0.01).

Trazodone Use for Sedation

Treating the pain and anxiety of pet animals is critical to patient satisfaction and quality of care. However, sedation is also necessary to facilitate handling and to allow clinical procedures to be performed correctly and safely (Clements, 2006) during veterinary visits (Gruen and Sherman, 2008; Orlando *et al.*, 2016). For hospitalized patients, trazodone is used commonly to eliminate the need for IV administration of sedatives, such as acepromazine and dexmedetomidine (Jay *et al.*, 2013).

There is recently published data on use of trazodone for sedation in cats but no data available for dogs. A pilot study on laboratory cats receiving trazodone at 50, 75 and 100 mg PO (10.6-16.7, 16.0-25 and 21.3-33.3 mg kg⁻¹, respectively) and one placebo control indicated that trazodone was likely well tolerated in cats and caused appreciable sedation at all doses. Sedation as measured by activity reduction was 83%, 46% and 66% at the doses of 50, 75 and 100 mg, respectively. Mean peak sedation ranged from 1-3 h after dosing and no severe or mild adverse responses were found. Only struggling, aggression and vocalization were noted (Orlando *et al.*, 2016). However, because the examinations were performed before the time of the pharmacodynamics peak, the sedation effect could be larger if the assessment was performed later. Some limitations were

observed in this study; not all doses of trazodone were randomized, subjects were limited to neutered male cats, cats were housed in a single room with visual access to the other cats and one cat did not receive a full dose on one treatment day (100 mg). In addition, the treatment was voluntarily ingested rather than being administered and not all cats received the medication in similar types or amounts of food. These limitations may have slightly altered absorption rates of trazodone, observations on animal behavior and measurements recorded (Orlando *et al.*, 2016).

Although it has not been studied in dogs, it is reported that trazodone at the initial target dose administration can cause sedation in some dogs if administered at more than a half of the initial target dose based on animal weight (Gruen and Sherman, 2008).

Trazodone Pre-Operative Use

The pre-operative use of trazodone has been less well documented in literature, however it is commonly used, off-label, for this practice (Gilbert-Gregory *et al.*, 2016; Murphy *et al.*, 2017). Veterinary hospitals are using trazodone to pre-medicate dogs in combination with opioid agents (Murphy *et al.*, 2017) but no information is reported in cats yet. In a prospective study in hospitalized dogs undergoing general anesthesia for orthopedic surgery, trazodone (5-7 mg kg⁻¹ dose), when used in combination with upload drugs, showed similar cardiovascular effects compared to acepromazine (Murphy *et al.*, 2017).

Trazodone Use for Post-Operative Confinement

Stress caused by a visit to the veterinary clinic has been highlighted to have negative impacts on animals, owners and veterinarians. Furthermore, the additional stress of surgery and the possibility of an extended stay in the veterinary hospital wards can increase the recovery period and can be of concern for the pet animals' welfare (Gruen *et al.*, 2014). In dogs especially if young, active, healthy and unaccustomed to confinement, the implementation of postsurgical instructions are often challenging to owners and sometimes for veterinarians as well (Gruen *et al.*, 2014; Guthrie *et al.*, 2012). This likely applies to cats as well. Consequently, failure to comply with activity restriction may lead to protracted recovery or even surgical treatment failure possibly requiring a second surgical procedure (Knudsen *et al.*, 2012). Trazodone is administered orally for acute and chronic anxiolysis to facilitate cage rest and activity restriction in dogs after orthopedic surgery (Jay *et al.*, 2013) and as well as for pre- or post-surgery of stress or anxious dogs during subsequent hospitalization (Gilbert-Gregory *et al.*, 2016).

A recent study on 36 client-owned dogs (19 females and 17 males; 3.0±2.46 year-old and 32.0±10.6 kg body

weight) that underwent orthopedic surgery and were treated with trazodone for 4 weeks combined with a short tramadol treatment (discontinued after 3 days), antimicrobials and other medications showed that trazodone moderately to markedly improved confinement tolerance and calmness. Median onset of action of trazodone was 31-45 min and median duration of action was ≥ 4 has reported by owners. Trazodone was administered at a dose of 3.5 mg kg⁻¹, PO, q 12 h combined with tramadol for three days. After three days, the trazodone dose was increased to approximately 7 mg kg⁻¹, PO, q 12 h. If needed, trazodone dose was increased from 7 to 10 mg kg⁻¹, PO, q 8 h. Furthermore, the increased trazodone dose (n = 25) dogs did not differ in age and weight compared to the standard treatment dogs (n = 11) (Gruen *et al.*, 2014). Although trazodone improved tolerance and calmness after surgeries, adverse events were observed in 55.5% of patients and included soft stool, constipation, thirst, restlessness/agitation, aggression, moaning, drowsiness, somnolence, panting, teeth chattering, drooling, paranoia and incontinence (Gruen *et al.*, 2014).

To date, no reports have been published for the use of trazodone for post-operative confinement in cats. However, it could be suggested for cats as trazodone is used effectively in dogs for post-operative confinement.

Trazodone Safety on the Cardiac System

Trazodone is as antidepressant and anxiolytic drug that at clinical doses produces very few cardiovascular side effects in humans (Munday *et al.*, 1975). A study reported that 0.3, 3 and 3 to 10 mg kg⁻¹ of trazodone lowered arterial blood pressure, slowed heart rate and reduced myocardial contractile force respectively, unlike imipramine (a TCA drug) (Gomoll *et al.*, 1979). Another report examined the effects of trazodone on several aspects of cardiac conduction compared to imipramine over a dose range 1-30 mg kg⁻¹, IV. This study revealed that trazodone promoted no evidence of heart block or sign of rhythm disturbances other than slowing in normal sinus rhythm when compared with imipramine in closed-chest pentobarbital-anesthetized adult dogs (Gomoll and Byrne, 1979). The last report aimed to evaluate the effects of trazodone on intracardiac condition in the anesthetized dog compared to imipramine, this indicated that trazodone lowered heart rate and prolonged the Q-Tc interval potentially suggesting greater safety of trazodone as a new and distinct antidepressant drug (Je and Aw, 1982).

Conclusion

Trazodone is approved by the FDA for the treatment of depressant and anxiolytic disorders in humans. However, trazodone has been legally prescribed by veterinarians as an off-label drug in dogs and cats. Its

pharmacological effects have been reported to reduce anxiety, behavioral stress, sedation, pre-and post-operation stress and do not affect cardiac conditions in dogs and cats in context of promoting animal welfare.

Trazodone's beneficial effects and common use have been reported on small sample sizes in relatively few clinical trials. Larger and randomized controlled clinical trials are necessary to soundly illustrate its efficacy in treating the diverse conditions for which it is used in clinical practice. Other studies would also need to demonstrate the risk and benefit ratio in different conditions for which trazodone has been prescribed. It is anticipated that this review will provide veterinarians with the information that they need to feel comfortable in prescribing trazodone for various off-label behavioral and medical conditions in dogs and cats.

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Author's Contributions

Bunna Chea: Contributed to the searching the literature and the writing of the manuscript.

Mario Giorgi: Contributed to the ideas and the writing of the manuscript.

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