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Trazodone: a multifunctional antidepressant. Evaluation of its properties and real-world use

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Trazodone is indicated for the treatment of Major Depressive Disorder (MDD), often associated with anxiety, insomnia, agitation, nervousness, or irritability.

The aim of this review was to summarise the pharmacological properties of trazodone in improving depressive symptoms in elderly patients and in patients with neurological comorbidities, for whom secondary depression is often present.

Five different pharmaceutical formulations of trazodone are available: intravenous or intramuscular liquid solution, immediate-release tablets (I.R.), oral drops, prolonged-release tablets (P.R.), and extended-release Contramid® tablets (COAD). The initial dose of trazodone should range from 75 to 100 mg/day. For COAD formulation, the starting recommended dose is 150 mg once daily. In elderly patients, trazodone may be administered at very low dosages (25-50 mg/day for I.R. formulation, and 50-100 mg for the P.R. or E.R. formulations). The maximum daily dose should not exceed 300 mg/day, split over two administrations across the day.

In elderly patients, trazodone has reported excellent results, keeping high-quality standards for safety and tolerability. It can help to improve insomnia and anxiety without resorting to benzodiazepines. In patients with neurological conditions, trazodone helps to treat anxiety-depressive symptoms. In patients with Alzheimer's disease or frontotemporal dementia, trazodone can help to handle behavioural symptoms, also acting as a putative neuroprotective agent.

Trazodone is well tolerated. Somnolence/sedation, dizziness, constipation, and blurred vision are common side effects with an incidence slightly greater than 5%. Orthostatic hypotension and headache are relatively common side effects.

The great availability of formulations allows to personalise trazodone administration according to patient profile characteristics.

Key words: trazodone, major depressive disorder, neurological disorder, geriatric population, insomnia

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INTRODUCTION

Trazodone is indicated for the treatment of depression and has been shown efficacious in reducing most symptoms associated with depression [1-3].

The peculiar multifunctional pharmacological profile of trazodone explains its efficacy to improve Major Depressive Disease (MDD), a very heterogeneous condition often associated with anxiety, insomnia, agitation, nervousness, or irritability [2,4-6]. To diagnose MDD, an individual must be experiencing five or more symptoms (Tab. I) during the same 2-week period. At least one of the symptoms should be either depressed mood or anhedonia [7].

All DSM criterion symptoms, except depressed mood, comprise at least two sub-symptoms, and three of the criterion symptoms (sleep, weight/appetite, psychomotor) can be met by either increases or decreases. Therefore, up to 16,400 possible symptom profiles can generate a diagnosis of MDD [8]. Furthermore, the transdiagnostic determinants and the DSM-5 specifiers (e.g., with anxious distress or with psychotic features) generate a much higher number of clinically relevant profiles [9,10].

Recent studies investigated the efficacy of particular antidepressants in improving symptoms for specific phenotypical profiles, thus showing how the selection of the best drug for a given cluster could be the new personalised approach for depression [11].

In such context, trazodone can represent an efficacious treatment for the geriatric population.

In the elderly population, the risk of depression is high[12]. In patients with one or more chronic illnesses or disabling conditions, secondary depression can be induced by pharmacological treatments[13]. Furthermore, depression can aggravate the chronic disease and *vice versa* could be exacerbated by the chronic disease itself. For example, heart disease and depression can be reciprocally worsened.

Symptoms of depression in the elderly differ from those in the young. Sleep disturbance and agitation may prevail in elderly patients. Other symptoms, as confusion or impaired attention, may be misinterpreted as a neurological disorder (i.e., Alzheimer's disease).

In patients with neurological conditions, secondary depression is common. Epilepsy, stroke, Parkinson's disease, and other neurological illnesses reported a high prevalence of secondary depression. Sleep disorder, fatigue, poor concentration, or disturbed appetite are also present. Antidepressants may improve symptoms, quality of life, and overall survival in patients with neurological disorders [14]. The aim of this narrative review was to summarise the pharmacological properties of trazodone in elderly patients and patients with neurological comorbidities. Moreover, this work also investigated trazodone efficacy on some specific symptoms as sleep disturbance, anxiety, agitation, and substance abuse. Two case reports were reported.

Table I. MDD Symptoms.

Depressed mood most of the day
Diminished interest or loss of pleasure in almost all activities most of the day (anhedonia)
Significant weight change or appetite decrease or increase nearly every day
Sleep disturbance (insomnia or hypersomnia)
Psychomotor agitation or retardation nearly every day
Fatigue or loss of energy nearly every day
Feelings of worthlessness nearly every day
Diminished ability to think or concentrate; indecisiveness nearly every day
Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Trazodone is a Serotonin Receptor Antagonist and Reuptake Inhibitor (SARI) [2] due to its affinity profile for the serotonin reuptake transporter (SERT) and serotonin receptors [15]. Trazodone behaves as a potent antagonist of 5-HT_{2A} and 5-HT_{2B} receptors, an antagonist of 5-HT_{1D}, 5-HT_{2C}, a_{1A}, a_{2C} H_1 receptors with moderate affinity, a partial agonist of 5-HT_{1A} receptors, and an inhibitor of SERT (Tab. II). At therapeutic dose, trazodone has no activity at muscarinic cholinergic receptors, dopamine receptors, and dopamine or noradrenaline transporters. Similar to other antidepressants, it inhibits serotonin reuptake [16].

The multi-target profile of trazodone provides the following clinical advantages:

1 The partial agonist activity at 5-HT_{1A} receptor may facilitate desensitisation of 5-HT_{1A} receptors in serotonergic projecting neurons of the dorsal raphe nucleus, thereby allowing a rapid antidepressant action[17] and may contribute to the anxiolytic activity of trazodone, as suggested by preclinical studies [18];
2 5-HT_{2A} and 5-HT_{2C} receptor blockade may limit the incidence of sexual dysfunction, usually associated with serotonergic drugs [19];
3 Antagonism at 5-HT_{2A}, $\alpha_{1A,}$ and H_1 receptors confer sedative and hypnotic properties [20,21]. Trazodone may treat the symptoms of hypoactive sexual desire disorder and antidepressant-associated sexual dysfunction because of its 5-HT2 antagonism [22-24];

Table II. Pharmacodynamic profile of trazodone.

Receptor	Ki (nM)	Effects
SERT	367.3	Antagonist
5-HT_{1A}	118	Partial agonist
5-HT_{1D}	106	Antagonist
5-HT_{2A}	35.8	Antagonist
5-HT_{2B}	78.4	Antagonist
5-HT_{2C}	223.9	Antagonist
α_{1A}	153	Antagonist
α_{2C}	155	Antagonist
H_1	220	Antagonist

Source data: Psychoactive Drug Screening Program (PDSP) database. K_i values are inversely proportional to the binding affinity of the drug for the target

4 The moderate affinity for 5-HT_{2C} and H_1 receptors may limit the risk of weight gain.

Pharmacokinetics

To date, at least five different pharmaceutical preparations of trazodone are available in the European Union (E.U.) or USA markets: 1) intravenous or intramuscular liquid solution, 2) immediate-release tablets (I.R.), 3) oral drops, 4) prolonged-release tablets (P.R.), and 5) extended-release Contramid® tablets (COAD).

Some pharmacokinetic parameters (C_{max}, T_{max}, and elimination half-life $t_{½}$) could differ according to the drug formulation (Table III). Trazodone is extensively metabolised by CYP-450 3A4. More than 99% of bioavailable trazodone is converted *via* oxidative cleavage to meta-chlorophenylpiperazine (mCPP), an active metabolite further metabolised by CYP2D6 [25]. Meta-chlorophenylpiperazine concentrations *in vivo* range from 1 to 20% of those of the parent drug [26]. Thus, the contribution of mCPP to the overall clinical activity is unclear. Trazodone has shown a serum protein binding of 90-95%, resulting in a bloodstream free fraction of 5-10%. Elimination predominantly follows the renal route. Trazodone pharmacokinetics approximates a two-compartment distribution model [20]. Because of its hydrophobic features, this compound easily binds to fat tissues and crosses cell membranes [27]. The oral bioavailability of trazodone is mostly affected by food. C_{max} value increases by 86% when the drug is administered with food [28].

DOSAGES

General recommendations

According to EMA guidelines, the initial dose of trazodone should range from 75 to 100 mg/day, administered in a single dose before bedtime. Dosage should be adjusted accordingly to clinical responses, up to 300 mg/day, split over two administrations across the day. Trazodone reaches the steady-state levels in about two days. The recommended starting dose of COAD is 150 mg once daily in adults. The dose may be increased by 75 mg/day every three days (i.e., start 225 mg on Day 4 of therapy). The maximum daily dose should not exceed 300 mg [29].

FORMULATIONS

The availability of different formulations (Table III) ensures the efficacy of trazodone in a wide range of

Table III. Pharmacokinetics.

Trazodone	Formulations	Cmax	Tmax	t1/2	Food interaction
TZ_{IR}	50 mg tablets 100 mg tablets 25 mg/ml drops 60 mg/ml drops	1.2-1.6 µg/ml	1 h (1.5 h elderly)	6.6 h (9-11 h at steady state)	Slow absorption
$TZ_{IV/IM}$	50 mg/5 ml solution for injection	NA	Immediate	6-8-h	No effect
$TZ_{PR\ film\text{-}coated}$	75 mg tablets 150 mg tablets	0.7-1.2 µg/mL	4 h	12 h	No effect
TZ_{COAD}	150 mg tablets 300 mg tablets	~ 1.5 mg/L (steady state) 2 ± 0.635 µg/mL	7.57± 2.3 h	10 h	Increased absorption Administration of TZ_{COAD} 300 mg once daily provides equivalent steady-state exposure to, with a lower C_{max} than, TZ_{IR} 100 mg given 3 times a day. A high-fat meal increases C_{max}, but there is no substantial effect on AUC.

TZ: trazodone; IR: immediate-release; IV: intravenous; IM: intramuscular; PR: prolonged-release; COAD: extended-release Contramid®

clinical scenarios. For example, the immediate-release (I.R.) formulation (available as tablets or liquid drops) reaches maximum blood levels in about an hour, ensuring rapid effects for symptoms like insomnia [22]. The relatively short elimination half-life (6h) reduces the risk of morning drowsiness [30]. The prolonged-release (P.R.) formulation is characterised by a film coating, which ensures slow release into the bloodstream. The extended-release (COAD) formulation provides an even more gradual and continuous absorption of the drug into the bloodstream. It allows a simplified once-a-day prescription schedule, thus enhancing adherence, improving tolerability, and avoiding see-sawing blood concentration patterns [30].

REAL WORD ISSUES & EXPERT OPINION: IDEAL TARGETED DISORDERS FOR TRAZODONE

Depression in elderly patients

Trazodone is clinically useful in elderly patients, including people with agitated behaviour, because of its specific anxiolytic and sleep normalising effect and excellent safety and tolerability [31]. In elderly patients, a very low starting dose is recommended, usually no more than 25-50 mg/day for the I.R. formulation or 50-100 mg for the P.R. or E.R. formulations. However, ageing does not significantly impair liver metabolism by CYP3A4, while the reduced renal clearance may increase trazodone blood concentrations [32].

When treating elderly patients, the once-a-day COAD formulation may be the best choice to rapidly reach therapeutic doses while minimising side effects (i.e., orthostatic hypotension). The liquid formulation may be preferred if dysphagia or other difficulties in administration are present. Drops may represent an advantage when small dosage changes are necessary. The rapid peak effect of the I.R. formulations (drops or tablets) also enables appropriate insomnia management. In our experience, most elderly depressed patients improve with doses as low as 100 mg/day. Finally, the dual action of trazodone on anxiety and depression is particularly useful to reduce benzodiazepines, which are burdened by several risks in elderly patients.

Depression with neurological comorbidities

Special populations such as depressed elderly patients may also be at high risk of dementia and cognitive impairment, for which depression has been reported as a risk factor or an early harbinger [33]. Trazodone helps to treat anxiety-depressive symptoms associated with subcortical dementias, Parkinsonism, and movement or behavioural disorders. It may be efficacious in treating behavioural symptoms of Alzheimer's disease [34] and frontotemporal dementia [35]. Interestingly, trazodone might cause neuroprotection by inhibiting the pancreatic endoplasmic reticulum kinase and eukaryotic initiation factor-2a (PERK/EIF-2a) unfolded protein response pathway [36]. Sustained activation of this pathway, which is associated with Alzheimer's disease, frontotemporal dementia, and other neurodegenerative disorders characterised by protein misfolding [37-39], causes translation repression, with ensuing neurodegeneration [36]. This unique property of trazodone suggests that this drug might be particularly valuable for treating depression associated with insomnia in patients with chronic neurodegenerative disorders, particularly in the early phases of neurodegeneration. In neurodegenerative disorders, trazodone behaves as a putative neuroprotective agent because it may promote the secretion of neurotrophic factors from cultured human astrocytes [40].

Furthermore, the absence of anticholinergic effects of trazodone is a further advantage in treating depression associated with Alzheimer's disease. The use of tricyclic antidepressant drugs and several antipsychotic agents in Alzheimer's disease is seriously limited by the anticholinergic activity of these drugs, which may further impair cognition [41,42]. On the contrary, recent retrospective analysis has reported an association between trazodone treatment and delayed cognitive decline in a sample of patients affected by Alzheimer's disease[43].

Depression with sleep disturbances

Insomnia is a condition that could significantly impact daytime activities because of a change of the sleeping pattern (difficulties with falling and staying asleep or waking too early). While primary insomnia has an unknown aetiology, secondary insomnia is usually induced by psychiatric or physical conditions or some external factors. There is strong evidence about the effectiveness of trazodone in the treatment of both primary and secondary insomnia [44]. Trazodone improves sleep mainly by increasing total sleep time, enhancing delta sleep entry, and decreasing the number of night-time awakenings [45]. It maintains these qualities in healthy and depressed-insomniac patients [46,47]. However, the antidepressant efficacy of trazodone seems unrelated to the severity of insomnia at baseline [2]. Roth et al. (2011) observed that a 50 mg dose of trazodone required one week to ameliorate the delta sleep phase, while 100 mg showed a positive effect after 1-2 days [48].

Depression in comorbidity with other conditions

Agitation and behavioural disturbances

Depressed patients can manifest verbal or physical aggressiveness, especially if anxiety symptoms,

depressive episodes with mixed features, or comorbid dementia are present [49,50]. Conversely, elderly patients with dementia who manifest physical or verbal aggression showed a higher prevalence of depression [51]. Trazodone inhibits aggressiveness [52], probably due to its association of a combined serotoninergic antidepressant activity and H1 histamine receptor blockade at low doses (i.e., 50-75 mg/day). Other drugs used to treat aggressive behaviour associated with depression (e.g., benzodiazepines) may cause falls, tolerance, physical dependence, and cognition impairment. Moreover, post-stroke patients often display depressive symptoms with emotional and behavioural changes such as anger, hostility, and impulsivity[53]. Of note, trazodone showed beneficial effects at 300 mg/die in post-stroke depression [54].

Preclinical findings have hypothesised that trazodone may restrain L-DOPA-induced dyskinesia and psychosis-like behaviours in Parkinson's disease [55]. Trazodone administration was also beneficial in a sample of bipolar inpatients affected by psychomotor agitation [56]. Other studies showed a good efficacy of trazodone in patients with agitation[57] and antipsychotic-induced akathisia [58].

Depression and anxiety

A large body of evidence supports the value of trazodone for treating generalised anxiety disorder [59] or post-traumatic stress disorder (PTSD) [60]. In both conditions, trazodone improved sleep disturbances [5]. It may be of particular help in patients with anxiety disorders who are at risk for benzodiazepine abuse [5].

Depression and substance abuse induced sleep disturbance

The reward deficiency syndrome that includes both dysphoric and depressive symptoms may appear after cocaine detoxification. A 9-patient study about X.R. trazodone formulation for the treatment of cocaine withdrawal symptoms has hypothesised that trazodone may improve the reduction of craving and reduce psychological symptoms, although its efficacy to avoid early relapse should be further confirmed [61].

Depression is commonly represented in substance abuse and usually unrecognised. Proper diagnosis of mood disturbance could prevent episodes of relapse and reduce suicide rates in this patient population. It would be necessary for routine clinical practice to recognise if a patient has primary or substance-induced depression to avoid treatment delay [62].

Sleep disturbance is frequent during alcohol withdrawal. A randomised, double-blind placebo-controlled trial showed that low doses of trazodone could improve sleep quality during alcohol withdrawal. However, the effect was lost once trazodone was discontinued [63].

Safety and tolerability

Trazodone is well tolerated in MDD patients [2,22]. The most common side effects are somnolence/sedation, dizziness, constipation, blurred vision. The incidence of these side effects is greater than 5% and is double that of placebo [64]. Other bothersome or relatively common side effects include orthostatic hypotension and headache [2,22,65]. Orthostatic hypotension may be more severe if an antihypertensive agent is associated. In the geriatric population, falls may occur more frequently [66,67].

Priapism is a rare adverse effect, likely due to α-adrenergic receptor blockade [66,68,69]. Trazodone should be used with caution to reduce the risk of priapism in patients affected by multiple myeloma, sickle cell anaemia, hypercoagulable states, leukaemia, autonomic nervous system dysfunctions, and anatomical deformation of the penis (e.g., Peyronie's disease, angulation, or cavernosal fibrosis), or in combination with SSRIs, cocaine, or atypical antipsychotics [2,70].

How to manage the adverse effects of trazodone

Orthostatic hypotension and dizziness

Trazodone has an excellent cardiovascular safety profile [71], although mild orthostatic hypotension can occur. Therefore, it is recommended to measure blood pressure before administration and advise the patient to remain seated or in bed for at least 30 minutes after administration and not to change position too quickly.

A recent investigation on a small sample of real-world elderly depressed patients reported no significant associations between QTc variations and trazodone administration [72]. Trazodone may also cause dizziness, which is a consequence of α-adrenergic receptor blockage, and usually occurs when large doses of the drug are taken on an empty stomach [65]. Due to the inhibition of small muscle contraction, patients may have a subjective feeling of losing balance and dizziness in more severe cases. In such cases, patients should lay down, rest, and avoid rapid movements. Proper hydration is recommendable, avoiding caffeine, nicotine, or alcohol [73].

Headache

Trazodone may induce headache. This effect is mediated by the active metabolite, mCPP, which, as opposed to trazodone, acts as an agonist at various serotonin receptors and may also enhance serotonin release [74]. Trazodone-induced headaches may not respond to conventional analgesics, and, therefore, can only be managed by suspending the treatment [75].

Sedation

Sedation during daytime sleepiness is a common adverse effect of trazodone [76]. Daytime sleepiness

might contribute to fatigue, decreased quality of life, and increased risk of occupational or car accidents [77]. Dosage adjustments, change in trazodone formulation (e.g., switching to the I.R. formulation, administered in the evening), and behavioural interventions, such as going to bed early [78], can improve symptomatology.

Gastrointestinal symptoms

Nausea and other gastrointestinal symptoms may occur if the agent is taken at high doses on empty stomach. Thus, taking trazodone with food is recommended [65]. For dry mouth, the use of oral lubricating gels, artificial saliva, or chewing gum might help to enhance salivation [79].

Overdose

Trazodone is a safe drug. Doses of 500 mg per kg are lethal for experimental animals. In contrast, doses as high as 10 g may not cause death in humans [65]. High doses of trazodone may seldom cause serotonin syndrome, a life-threatening condition due to serotonin accumulation [80]. The most common systems involved in trazodone overdose are respiratory, cardiovascular, nervous, and gastrointestinal systems [81].

At toxic blood concentrations, trazodone may cause prolongation of Q.T. interval and torsade de pointes. Cases of life-threatening cardiac arrhythmias have been reported even at regular doses. Concomitant use of trazodone with drugs known to prolong the Q.T. interval or causing cardiac toxicity should be avoided [2].

Contraindications - warnings

Trazodone should not be used in combination with monoamine oxidase inhibitors (MAOIs). Caution is needed when trazodone is co-administrated with drugs that increase serotonin levels for the potential risk of serotonin syndrome [82].

In patients with liver failure, trazodone should be avoided [83]. It should not be used during intoxication with alcohol or hypnotic agents or in patients with myocardial infarction [84].

CASE SCENARIOS

Case 1: depression in patients with neurological disorders

A 51-year-old woman, divorced, without sons, was diagnosed with multiple sclerosis. Since she lost had her job, she experienced a depressed mood, sleeping problems, apathy, difficulty performing daily activities, and increased appetite. She also complained of anxiety, aggravation, restlessness, muscle tension, poor concentration, and fatigue. Her primary care physician prescribed her clonazepam, which she gradually increased up to 8 mg/day without consulting her doctor. After two years, since she reported depressed mood, severe anxiety, poor concentration, poor memory, increased appetite, and suicidal thoughts, she was hospitalised. X.R. trazodone 150 mg, to be taken before bedtime, was prescribed. Clonazepam was gradually decreased to 6 mg on day 1, 4 mg on day 2, 3 mg on days 3 and 4, 2 mg on days 6 and 7, and 1 mg on days 8 and 9, followed by discontinuation. During hospitalisation, the patient also received intensive psychotherapy. After three days, trazodone was increased to 225 mg, and after another three days, the dose was further increased to 300 mg. She showed a gradual improvement in mood, anxiety, and cognitive functions. Trazodone was also combined with prolonged-release quetiapine to improve mood and anxiety. Quetiapine was started at 50 mg, to be taken in the morning, and gradually increased up to 200 mg, always to be taken in the morning. Two weeks after discharge from the hospital, the patient complained about moderate daytime sleepiness, which improved after discontinuing quetiapine. COAD trazodone was continued at 300 mg in the evening. Excellent results were reported.

Case 2: depression in a geriatric patient with cognitive impairment

A 75-year-old widow with three sons showed mild attention deficit and difficulty planning actions, abstracting thoughts, and finding words and names for commonly used objects. In the following two years, her condition deteriorated significantly: memory loss, difficulty recognising familiar people and places, disorientation, inability to acquire new information, and a gradual tendency to neglect her hygiene and nutrition were registered. Therefore, she was admitted to an assisted health residence. Later, she experienced apathy, loss of interest, refusal to get out of her bed, reluctance to eat, insomnia, anxiety, depressed mood, crying spells, and pessimistic thoughts. After a thorough assessment, she was diagnosed with depression, comorbid to cognitive impairment. So far, memantine at the dose of 10 mg/day was administered. Later, COAD trazodone 150 mg, half tablet to be taken in the evening, was prescribed. After three days, her insomnia and anxiety improved, and no side-effects were reported. She started to eat again. COAD trazodone was increased to 1 tablet in the evening with a progressive and clear-cut improvement of sleep, anxiety, mood, appetite, and interests. After about five weeks of trazodone treatment, the patient was completely free of depressive symptoms.

CONCLUSIONS

Major depressive disorder is a great public health challenge, the leading worldwide cause of disability. The complexity and heterogeneity of this condition have always been the object of clinicians. Many efforts have been made to identify antidepressants and personalised formulations in improving symptoms according to the different patient profiles. There is evidence that a range of depressive patient profiles, including elderly patients and those with underlying neurological conditions, sleep disturbance, agitation, or substance abuse, may benefit from trazodone.

The efficacy, safety, and tolerability of trazodone are widely proven. Different formulations allow personalised treatments, thus improving specific symptoms associated with depression MDD, like insomnia, anxiety, agitation, or nervousness. The COAD formulation offers the advantage of once-a-day administration and the possibility to start with a dose (150 mg) that is already potentially effective for depression, along with a steady, gradual release of the medication in the bloodstream throughout 24 hours. The PR formulation offers the advantage of an evening administration (up to 150 mg) for patients (e.g., those with middle and late awakenings) who need drug exposure during the night and a maximum blood concentration at approximately 4 hours from drug intake. The I.R. formulation offers the advantage of reaching the maximum blood concentration after 1-2 hours, and this is particularly valuable for depressive patients with initial-early insomnia. Intravenous and intramuscular formulations have immediate or quick absorption, respectively. These advantages are particularly useful in patients with depression and psychomotor agitation. Intravenous and intramuscular formulations help patients with poor adherence or inability (e.g., post-surgery) to take oral medications. Trazodone displays a good tolerability profile, with a low risk for weight gain, sexual dysfunction, and anticholinergic effects such as dry mouth, constipation, and urinary retention. Finally, the PERK/EIF-2a pathway inhibition suggests trazodone as a potential neuroprotective activity in chronic neurodegenerative disorders characterised by protein misfolding, such as Alzheimer's disease, in which comorbid depression complicates the management of patients.

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