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Prion diseases motor and neuropsychiatric symptom cluster pharmacotherapy: structured scoping review

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Abstract

Background

Prion diseases are a group of rare, neurodegenerative conditions which are invariably fatal and cause a variety of symptoms which can prove challenging to control. Through this paper we aim to review the current evidence regarding pharmacological management of neuropsychiatric and motor symptoms of prion disease, as well as draw on experts' and relatives' experience, to evaluate the current evidence and provide recommendations moving forwards.

Methods

A scoping review of the literature for pharmacological management of symptoms was conducted using the systematic review tool, COVIDENCE, with searches conducted through 4 databases. 120 papers were selected for inclusion, and data extraction was carried out by 2 independent reviewers. Given the lack of high-quality data and small numbers, no further attempt at statistical analysis was made, and results are presented in a thematic synthesis.

Results

Although a broad range of approaches and pharmacotherapies are trialled to manage these challenging symptoms, there are patterns emerging of some efficacy seen with the use of benzodiazepines, anti-psychotic, and anticonvulsant medications in both motor and neuropsychiatric symptoms in prion disease. These approaches and associated challenges were reflected in international expert opinion that was gathered via online survey.

Conclusion

There continues to be a paucity of good quality evidence and we suggest a need for longitudinal, population-based and standardised research to allow a robust evidence base which in turn will guide excellent symptom control and end of life care for this group of complex patients.

Key Messages

What is already known on this topic

There is a lack of consensus or clear guidance as to pharmacological management of symptoms in prion diseases.

What this study adds

This study confirms a lack of high-quality research or guidance, though does attempt to highlight some patterns emerging from the literature and expert opinion as to approaches being used in management of neuropsychiatric and motor symptoms.

How this study might affect research, practice, or policy

We suggest a need for further high-quality research to enable development of clear guidance for clinicians for symptom management and for caring patients with this rare and challenging group of conditions.

Introduction

Prion diseases, characterised by their rapid progression and invariably fatal outcomes, present significant challenges in management at the end of life. The management of prion diseases is primarily symptomatic, with no current therapies available to halt or reverse the progression of the disease. This structured scoping review aims to systematically evaluate the pharmacological interventions used to manage the motor and neuropsychiatric symptoms associated with prion diseases. By integrating clinical experiences and best practice, this review aims to outline current therapeutic approaches whilst also identifying significant gaps in knowledge that future research must address.

Given the rarity and complexity of prion diseases, this review also incorporates expert opinion to further consider insights into practical management strategies that are not widely documented in the scientific literature.

Background

Prion diseases represent a constellation of rare and fatal neurodegenerative conditions. The causative agents of these disorders are abnormally-folded prion proteins, which induce a cascade of conformational change in the native cellular prion protein[1]. This cascade precipitates neurodegeneration. Prion malfunction and how they develop into disease-causing agents remains relatively poorly understood, however they are recognised as transmissible in both humans and animals. The aetiologies of human prion disease include sporadic, genetic, and acquired forms. Human prion diseases exhibit a breadth of symptoms of which the majority cluster into cognitive and neuropsychiatric symptoms, and motor impairment.

Sporadic Creutzfeldt-Jakob Disease (sCJD) is the most common subtype, accounting for 85% of individuals, with a worldwide annual incidence of 1–2 per million[2]. The mean age of onset of sCJD is 68 years, with recent papers describing the extremes of age[3,4]. The median survival is 4 months and 95% die within 12 months [5]. The classical presentation is a rapidly progressive cognitive decline with ataxia, myoclonus, and pyramidal/extrapyramidal signs. The pure visual presentation (Heidenhain presentation) has isolated cortical visual disturbances at onset, often followed by a relentless decline and shorter survival. The pure ataxic presentation often presents with a marked delay to cognitive decline, and may exhibit prolonged survival [6]. Pure cognitive presentations may have marked delay to onset of motor features. Pure psychiatric presentations can occur, with marked behavioural, personality, or affective symptoms. Additionally, psychiatric symptoms are common throughout the disease course, and those with a prolonged disease duration may have more complex psychiatric features[7–9]. The clinical phenotype is highly heterogenous.

Inherited prion disease (IPD) is responsible for 10-15% of human prion disease. IPD is the consequence of pathogenic mutations in the Prion Protein Gene (*PRNP*). The majority have an autosomal dominant pattern of transmission with high penetrance. These diseases are highly heterogenous, and often with an extended clinical duration. Historically, there have been clinical categories of inherited prion disease due to phenotypic presentations which include familial CJD (fCJD), Gerstmann-Sträussler-Scheinker (GSS), and Familial Fatal Insomnia (FFI). In reality, inherited prion diseases are best described by the mutation.

Variant CJD (vCJD) was the consequence of bovine-to-human transmission of bovine spongiform encephalopathy (BSE). The first case emerged in 1995[10], with 233 cases worldwide to date[11]. The UK represents 178 cases[11], with the last diagnosis in 2016[12]. The majority of vCJD cases are believed to be infected through dietary exposure of the bovine spongiform encephalopathy (BSE) agent[13], three UK cases are iatrogenic and attributable to blood transfusions, and the three most recent cases (Italy in 2016,

France in 2019, and France in 2021) have been plausibly linked to occupational exposures in prion research laboratories[14,15]. Variant CJD was characterised by a psychiatric onset, painful dysaesthesias, unusually young age of onset, and a unique neuropathological profile [16]. Iatrogenic CJD (iCJD) has most-commonly been described in recipients of implicated cadaveric-derived human pituitary hormones and dura mater grafts. iCJD has rarely been described in corneal graft recipients and those who have had intracranial instrumentation[17]. Human growth hormone-associated iCJD (hGH-iCJD) and human gonadotropin hormone-associated iCJD (hGNH-iCJD) presents with a progressive cerebellar syndrome with varying incubation periods ranging from short years to in excess of 40 years[18].

Variably Protease-Sensitive Prionopathy (VPSPr) is a rare sporadic human prion disease. At presentation, there are often psychiatric features, speech deficits, and/or cognitive decline with a predominately frontal syndrome. Motor features are common throughout the disease course, and the disease duration often exceeds 1 year[19]. Prion disease may not be suspected in these patients, and it can be difficult to differentiate from atypical non-Alzheimer dementias[19]. VPSPr may be underdiagnosed due to low suspicion of prion disease in life and investigations are not sensitive, MRI scans are often normal and RT-QuIC rarely yields a positive result[20].

Table 1 attempts to classify and distinguish between the human prion diseases, however it should be noted that this approach is most useful in diagnostics and research approaches. For patients dying of these diseases there is significant symptomatic overlap and classification is broadly of less value.

Table 1. Summary of Human Prion Diseases

Type of Prion Disease		Typical Presentation	Typical Age of Onset	Progression and Survival
Sporadic prion diseases	Sporadic CJD	Rapidly progressive dementia and ataxia, however, clinically heterogenous.	Median 68 IQR 63-74[3]	Median 4 months, IQR 2-8 months, range 1-132 months[21], 95% mortality within 12 months[3]
	VPSPr	Presents with psychiatric signs, cognitive impairment (frontal), and speech disturbance.	Median 70	Median 24 months[19]
Genetic prion diseases	Inherited Prion Disease	Clinically heterogenous, may mimic sCJD.	Typically, 50 years	Variable, depending on mutation
Acquired prion diseases	Variant CJD	Psychiatric symptoms, painful dysaesthesias, and delayed development of further features.	Acquired	Median 14 months, range 6-114 months[21]
	hGH-iCJD	A progressive cerebellar syndrome and delayed development of further features.	Acquired	Median 14 months, range 4-32 months[18].
	hDM-iCJD	A progressive cerebellar syndrome, or like classical sCJD.	Acquired	Median 15 months[22]

For many clinicians the rare incidence of prion diseases may mean they see only a small number in their entire career and thus familiarity with the type of phenotypes seen may be of use. Table 2 provides a series of vignettes describing prototypical cases, based on no single patient, but instead a cumulative picture of clinical signs and symptoms:

Table 2: Case Vignettes describing classical presentations and evolution of symptomatology

Sporadic CJD – Ataxic onset	A 60-year-old man presented to the emergency department and admitted to elderly care with 2-month progressive gait disturbance, limb incoordination, and new-onset slurred speech. In the past month, he has begun using a walking stick due to multiple falls. He can only use his left hand for eating, shaving, or reaching for objects due to a tremor on approach. His wife now sleeps in the spare bedroom due to frequent limb jerking throughout the night. In addition, there have been some concerns regarding his memory. Cognitive examination revealed deficits in memory and verbal fluency. Full neurological examination revealed cerebellar ataxia, right-sided hyperreflexia, and spontaneous and stimulus-sensitive myoclonic jerks. He was diagnosed with sporadic CJD following a supportive MRI head and positive CSF RT-QuIC. His relatively preserved cognition allowed him to express wishes for his future care, and he was able to work collaboratively with his palliative care team to facilitate discharge home, complete a ReSPECT form, and appoint a lasting power of attorney. He consented for PRNP genetic sequencing, which ultimately rule out inherited prion disease. He died 8 months later at home, with a total disease duration of 10 months.
Sporadic CJD – Heidenhain onset	A 78-year-old woman presented to the opticians with 2-weeks of progressive visual disturbance. She experienced visual distortion, colour misperception, and visual illusions. She was cautious navigating her house and described wonky doors and uneven floors. She thought her husband had bought new curtains as she misperceived them as bright pink. She described seeing insects, but these were illusionary phenomena of dust and smudges. The optician assessment was unremarkable and she was advised her to see her GP. In the subsequent week, she developed visuospatial and memory deficits. She became unable to tie laces, fasten buttons, or use keys or cutlery. She became forgetful and repetitive. She lost insight into her visual problems and developed significant paranoia and distress regarding an insect infestation. The GP referred for an urgent assessment under the Mental Health Act, which subsequently resulted in her admission under section 2. Over the next week, she developed hyperreflexia, hypertonia, and myoclonus. She was accepted for direct admission under neurology for a suspected organic cause. On admission, she was now akinetic mute with cessation of oral intake. Her MRI showed multifocal cortical ribboning and her CSF was unreactive. She was given a diagnosis of sporadic CJD and referred to palliative care. She died in hospital one week later, with a total disease duration of 5 weeks. Following her death, CSF RT-QuIC was reported as positive. Her family did not choose to proceed with *PRNP* genetic sequencing.
Sporadic CJD – Classic	A 68-year-old woman presented to the emergency department and admitted to general medicine with a 2-month history of memory difficulties and personality changes. She became forgetful by missing appointments and misplacing items. She started double locking the doors, and repetitively checking that this had been done. She developed mild paranoia that her belongings were being stolen. In the past 2 weeks, she has had balance difficulties and started using a stick. In the past 7 days, she has become increasingly disoriented and started having falls. Her family brought her to ED due to concern with the rapidity in her decline. Over the next month, her cognition and mobility declined. She could no longer hold conversation and remained bedbound. Examination revealed cerebellar ataxia, rigidity throughout, dystonic posturing of the left arm, and the occasional myoclonic

	jerk. A diagnosis of sporadic CJD was given following a supportive MRI head and CSF RT-QuIC. The patient was discharged to the local hospice. In hospice, the myoclonic jerks increased in frequency and amplitude which made personal care increasingly challenging. These were ameliorated with regular oral levetiracetam, which was eventually switched to midazolam via continuous subcutaneous infusion. She died a few weeks later, with a total disease duration of 4 months. The family consented to *PRNP* genetic sequencing which ultimately excluded inherited prion disease.
Inherited Prion Disease	A 50-year-old man presented to neurology outpatients with a 1-year history of lower limb sensory disturbance, limb incoordination, and wheelchair-use due to gait imbalance. Further history elucidated deficits to his memory, language, and some personality change. Examination revealed a mild cognitive impairment and cerebellar ataxia. His father developed a cerebellar ataxia at age 56, and later developed dementia and died at age 60, but there was no autopsy. His neurologist arranged CSF sampling, an MRI brain, and hereditary ataxia gene panel testing. Genetic testing revealed P102L mutation in the *PRNP* gene. He was given a diagnosis of P102L inherited prion disease. Subsequent MRI head was supportive, and CSF RT-QuIC was negative. His cognitive function deteriorated over the next few months, and he subsequently moved to a nursing home to receive his ongoing care. He developed behavioural issues that were not amenable to conservative measures. He was prescribed a short course of risperidone, which helped in the short term, but he experienced sedation. Disease progression made him increasingly withdrawn and apathetic, and he no longer experienced behavioural issues. He died in his nursing home, with a total disease duration of 3 years.
Iatrogenic CJD – HGH-associated iCJD	A 54-year-old woman was admitted with a 6-month history of progressive unsteadiness and a 2-month history of rapid cognitive decline. Between 1980-1985, she received regular intramuscular injections of cadaveric human growth hormone (hGH) for idiopathic short stature. Subsequently, she received notification that she was 'at increased risk' of CJD. She was given a diagnosis of hGH-associated iatrogenic CJD following a supportive MRI head and confirmation of her exposure. She was discharged to hospice. She died 2 months later, with a total disease duration of 8 months.

Diagnosis is reliant on clinical suspicion with characteristic features from the history and examination, international consensus diagnostic criteria, and supported by changes seen on MR brain imaging and cerebrospinal fluid RT-QuIC results [5,23]. A definitive diagnosis can only be achieved by neuropathological examination, although the autopsy rate in CJD in the UK is currently approximately 15% of cases[21]. Given this, it is important to bear in mind the potential impact on bereavement for loved ones where post mortem examination is pursued [24]. Due to diagnostic challenges, prion disease can be misdiagnosed as other neurodegenerative or primary psychiatric disorders, with delays to correct diagnosis contributing to family distress[25].

To date, there have been several disease modifying therapies trialled in CJD and other prion diseases without significant effect on mortality; including quinacrine, doxycycline, and flupirtine[26–28]. Current research shows some promising results. A study in mice demonstrated the role of antisense oligonucleotides in inhibiting prion formation and subsequently extending life by slowing disease progression[29,30]. Whilst promising in an animal model, a limitation is the need for intracerebral injection. Monoclonal antibody therapy demonstrated symptom stabilisation in patients with CJD for a short period of time[31].

The focus of management in this fatal group of disorders is on diagnosis, excluding treatable mimics, holistic symptom control with pharmacological and non-pharmacological methods, and palliative care.

In summary, Prion diseases are rare, often diagnosed late with rapid progression of symptoms which can be challenging to manage, and result in a patient experience that does not align with the cultural expectation of a “good death” in the UK[32]. There are well documented responses from social work[33] and nursing colleagues[34,35] but few studies have investigated the overall care needs of people with CJD or how these might be ameliorated or supported.

Multiple drugs are used to control symptoms in human prion diseases but the evidence base for most of these is spartan and to date there has been no review of the evidence for which drug class or individual agents to use in specific symptoms or symptom clusters. Those drugs that are in use are based largely on anecdotal and experiential evidence, but no pharmacological guidance is in existence to support clinicians in symptomatic management.

A palliative approach to patients with prion disease might include the following considerations:

- Diagnostic challenges
    - Diagnosis is complex due to non-specific early symptoms and the need for specialized tests, such as MRI and CSF analysis, for confirmation. Challenges include rapid disease progression which often outpaces timely diagnosis and initiation of palliative care.
- Early Integration
    - Palliative care should be integrated early in the disease trajectory from the onset of clinical suspicion without waiting for confirmatory diagnosis to manage symptoms effectively and improve quality of life.
- Symptom management
    - Focus is on managing neurological symptoms, cognitive decline, and physical complications. Expert management of these symptoms is crucial.
- Holistic Care
    - Palliative care should address not just physical but also psychological and spiritual needs, providing support to both patients and their families.
- Interdisciplinary Approach
    - Involvement of a multi-professional team including neurologists, palliative care specialists, nurses, and social workers aims to provide comprehensive care.
- Research and Development
    - Continuous development of guidelines and evidence-based practices is needed and an ongoing need for research to inform care strategies.

Aims & Objectives

In 2022 we wrote to the editor of BMJ SPCare to describe current practice across 3 large UK tertiary centres supported by the National CJD Research and Surveillance Unit. In that retrospective structured review of case records we demonstrated that half of people cared for with CJD had been transferred to a specialist or hospice setting, and the majority died in a hospice bed[36].

The case review highlighted symptoms in neuropsychiatric and motor clusters. The most common neuropsychiatric symptoms identified were agitation, challenging behaviour, hallucinations and anxiety, and between 1 and 5 separate medications were prescribed for agitation in any single patient. This implies challenging symptom control, and that no medication offered universal effect. Our findings correlate closely to other published reports which described that across all types of prion disease, cognitive impairment is the commonest neuropsychiatric symptom, followed by personality changes (~20%), affective illness (~14%), and psychosis/agitation (~11%)[37].

In our review, spasticity, ataxia and myoclonus were among the motor symptoms recognised, with multiple medications used in escalating doses implying challenging symptom control[36]. This reflects the published literature describing gait disturbances, myoclonus, and increased tone as the most frequently observed movement disorders in prion diseases with chorea, alien limb phenomenon, and nystagmus least frequently observed[38].

Not only are these symptoms commonly experienced but recent work has highlighted that symptoms related to movement and co-ordination as well as mood and behaviour are some of the most challenging for carers of those with prion disease[39].

We worked with the families of current and past patients supported by the National CJD Research and Surveillance Unit to understand their experiences of symptom management to inform our work. All gave consent for their words to be used and were keen to support any work that attempted to enhance the options for symptomatic support for patients with such disease. They were able to eloquently describe how challenging supporting someone with a prion disease is:

Family Member: "Everything is hard. Everything is now a challenge. The simplest of things now needs to be broken into its component parts and is frustrating, exhausting and time consuming."

The themes in their responses described the enormous impact of motor symptoms such as rigidity and myoclonus on completing basic activities of daily living, and the risk that is now encountered on attempting even basic mobility. They were also able to describe how the variable symptoms encountered and the lack of experience of managing such cases in local teams also exacerbated the situation:

Family Member: "Our experience of the symptoms of CJD were so varied and often unexpected. It felt very much like as soon as one symptom was effectively managed that either another symptom arose or the symptom trying to be managed seem to escalate faster than we could keep up with alterations of medication. This added to pressures and for us as family increased stressors, we felt local teams were ill equipped to identify, recognise and or treat majority of symptoms displayed and understand the fast progression and escalation of symptoms."

They described the challenge of requiring medications that were unfamiliar to local teams and thus there were often obstacles to prescribing, or to stock being available[40].

This lack of experience resonates with a recent poll of palliative care physicians attending a study day on General Medicine in 2022 which suggested that the majority (83%) had experience of providing care for a patient with a prion disease, but most of those (59%) saw these cases less than annually. A significant

majority (83%) found managing symptoms in these patients challenging[41]. However, the guidance that does exist to support clinicians in these situations remains vague and with minimal information on specific symptomatic treatment approaches[42].

Therefore, this inter-disciplinary working group from regional centres across the UK, comprising palliative care, psychiatry, and neurology doctors and nurses, including input from the UK National CJD Research and Surveillance Unit, aimed to understand the available evidence for, and current practice in the treatment of, the 2 largest and most troublesome symptom clusters – those of motor and neuro-psychiatric symptoms.

Aim

The aim of this structured scoping review is to evaluate the evidence for pharmacological interventions in the management of motor and neuropsychiatric symptom clusters in prion diseases, integrating clinical experiences and best practices from experts globally.

Objectives

1. Systematically review published studies and clinical trials that investigate the efficacy and safety of pharmacological treatments for motor and neuropsychiatric symptoms in prion diseases.
2. Gather insights on current clinical practices and therapeutic approaches from an interdisciplinary group of experts in palliative care, psychiatry, and neurology through a standardized online questionnaire.
3. Highlight areas needing further research and to suggest potential future directions for investigation and development.

Methods

A scoping review of the literature on pharmacotherapies for symptomatic management in prion diseases was conducted, adhering to the methodological framework originally proposed by Arksey and O'Malley[43]. The steps followed in this framework included: 1) identifying the research question, which focused on evaluating the evidence for pharmacological interventions in managing motor and neuropsychiatric symptoms in prion disease patients; 2) identifying relevant studies through a comprehensive search across multiple databases; 3) selecting eligible studies based on predefined inclusion and exclusion criteria; 4) charting data to organise and categorise information systematically; 5) collating, summarizing, and reporting results to highlight key findings and gaps in the current literature; 6) consultation with experts.

Given the scoping nature of this review, an in-depth quality appraisal of the included studies was not conducted. Broad inclusion criteria were used, recognising the rare nature of this illness. However, the limitations of the studies were acknowledged to provide context for the findings and guide future research directions.

A search strategy, tailored to the unique challenges posed by the rarity and complexity of prion diseases, was developed to gather the evidence for specific pharmacotherapies in the symptomatic management of:

1. Neuro-Psychiatric Cluster Symptoms
2. Motor Cluster Symptoms

This review specifically did not attempt to consider the literature and evidence for pharmacotherapy to treat or alter the course of the underlying prion disease which has been reviewed and presented elsewhere. Rather, this review focuses on symptomatic treatments to reduce symptom burden, improve quality of life and patient and family experience.

Papers were included based on the following:

- Population: Human participants diagnosed with any form of prion disease.
- Intervention: Studies focusing on pharmacological therapies aimed at symptom management.
- Comparators: Any comparative intervention was considered.
- Outcomes: Studies must describe the outcomes of symptom management, whether positive or negative.
- Study Design: All study designs reporting on pharmacological therapies were included.
- Language: No language restrictions were applied.
- Exclusions: Animal studies, non-prion disease-related research, studies not involving pharmacological therapies, and non-pharmacological interventions like nutritional strategies.

Anticipated small numbers of relevant papers meant that there was no plan to group studies for subgroup synthesis. The search strategy used MESH terms derived without language restrictions from:

a) The Neuropsychiatric Inventory (NPI) [44] and commonly prescribed drugs and drug classes
b) Motor symptoms listed in the European CJD Surveillance Network Criteria[23] for different types of CJD, as well as commonly prescribed drugs and drug classes.

The following 4 databases were searched; Web of Science, PubMed, Embase, and Medline with the final date of access being 1st of February 2024. This method attempted to encapsulate the unique nature of a rare but well characterised disease; namely that there are dozens of single case reports, a smaller number of case series, and no clinical trials or meta-analyses of drugs in the symptomatic management of human prion diseases. By keeping the search terms broad and accepting that this could incorporate many studies

that are not relevant and increase the work of checking if studies match inclusion criteria, it aimed to avoid missing studies.

The overall process of constructing the PRISMA diagrams and vetting studies was done via the systematic review tool COVIDENCE. Upon finalising the list of studies for inclusion, data extraction was performed using a structured approach to ensure consistency and completeness. 2 independent reviewers extracted data from each selected study using a predefined data extraction form, developed to capture detailed information relevant to the study's focus on prion diseases and palliative care. The data extracted included:

- Symptom Subtype: Identification of the specific symptom subtype addressed by the pharmacological treatment.
- Drug Name and Class: Documentation of the medication used, including both the generic name and the pharmacological class.
- Dose and Route of Administration: Detailed recording of the dosage and the method of administration prescribed. The route of administration is particularly relevant given that swallowing difficulties are universal in disease progression and avoidance of unnecessary intervention is a standard of end-of-life care. Dysphagia or loss of safe swallow is not a common feature of prion disease per se but is recognised in some inherited variants[45]. In cases where not all of the above were present, what was described was captured.
- Efficacy of the Medication: Assessment of the effectiveness of the pharmacological treatment as reported in the study, noting any quantifiable outcomes or qualitative observations.
- Side Effects Described: Description of any adverse effects associated with the medication, as described in the study.

In cases of disagreement between reviewers, conflicts were resolved through discussion or, if necessary, consultation with a third reviewer. This methodological rigor ensures that the synthesis of data is comprehensive and accurately reflects the scope of the literature on the pharmacological management of symptoms in patients with prion diseases. The synthesized data were then analysed descriptively, providing a robust foundation for understanding the efficacy and safety of the treatments employed.

Due to the small number of studies and the paucity of data no greater attempt to define relevant characteristics e.g. patient demographics were made. This means that there can be no assumptions made about subgroups of patients with prion disease e.g. stratified by age or by disease subclass and this may add heterogeneity to the results. Formal assessment of the quality of studies was not undertaken, but clear conflict of interest was assessed for at data extraction and not identified in any papers.

Results will be presented in a thematic synthesis given extremely small numbers.

Results

Preliminary findings of the reviews of pharmacological management of neuropsychiatric and motor clusters were presented at the European Association for Palliative Care World Congress in June 2023 and a full review subsequently completed.

The analysis of neuropsychiatric symptoms in prion disease included 90 papers. This comprised mostly of case series and reports, but did include 1 randomized control trial, 2 systematic reviews, and 6 opinion pieces, offering a broad overview of patient care across 696 cases. These papers predominantly discussed CJD and other inherited prion diseases. The timeframe of these publications ranged from 1974 to 2021, featuring contributions from a diverse international cohort, with the largest subset (30 reports) authored in the United States.

30 reports focused on the pharmacotherapy of motor symptoms in prion disease, predominantly in patients with Creutzfeldt-Jakob Disease (CJD), though also covering other inherited prion diseases. The dataset included case series, case reports, and review articles delineating best practices. These reports provided insights into the care of 74 individuals affected by prion disease. The publications spanned from 2001 to 2021 and were published by a spectrum of international authors with the most (7 reports) coming from the United Kingdom.

In both reviews the small numbers of cases presented, and lack of transferability means that no statistical analysis or meta-analysis was undertaken. These results can offer only a description of practice with some suggestions as to those medications being used more widely for such symptom clusters, with no clear guidance on how they might be employed, their risk of side effect or their efficacy.

Summary of results for Pharmacological Management of Neuropsychiatric Symptoms

90 studies were identified for review regarding pharmacological management of neuropsychiatric symptoms. The selection process and an overview of the main characteristics of the included studies can be seen in the PRISMA diagram shown in figure 1, and supplementary table 1.

Fig 1. PRISMA diagram – Pharmacological Management of Neuropsychiatric symptom

Supplementary Table 1: Included Papers in Review of Pharmacological Management of Neuropsychiatric Symptoms (grouped by study design).

Based on review of the included papers, descriptions were extracted of pharmacological management of neuro-psychiatric symptoms including anxiety, agitation and startle, mood disturbance, sleep disorders, psychosis, cognitive impairment and management of challenging behaviour. Multiple papers did describe additional symptoms including language disturbance (68), visual disturbance (23) and other altered sensory symptoms (27) but none described any symptomatic treatment for these phenomena.

Efficacy was reported where there was any commentary made about improvement in symptom intensity or frequency. These were broadly subjective statements with no quantification available. Details of the descriptions extracted can be seen in supplementary table 2.

Supplementary Table 2: Reported Pharmacological Management of Neuropsychiatric Symptoms

Supplementary table 2 demonstrates clearly that much useful data is missing and most papers describe mixed reports of efficacy or no positive effect. Many papers failed to detail the impact of the pharmacotherapy at all or failed to delineate indications around behaviour or symptom management when drugs might be used in multiple scenarios e.g. selective serotonin reuptake inhibitors (SSRIs) in depression or anxiety. In several circumstances pharmacotherapy was commenced when the diagnosis was felt to be psychiatric in origin, or in fact pre-dated prion symptoms as the patient had previous psychiatric diagnoses, and these have been included if they speak to symptomatic control. It should be further noted that the possible role of medication vs the underlying prion pathology in causing increased tone or motor abnormalities was often not explored leading to lack of clarity over the frequency of extra-pyramidal side effect profiles of these medications.

Where the rationale for prescription (e.g. in mixed symptomatology) was unclear and there was scanty reporting of therapeutic intervention, the details are not reported as they were felt to be unable to be interpreted. Where a class or group of drugs was described, this has been reported where it offered enough detail e.g. descriptions of SSRIs have been included but those papers who referred to “anti-depressants” have not as it was felt the potential inclusion was too broad to be useful.

Anxiety and agitation were described in 78 papers with a wide range of agents including antipsychotics, antidepressants, and sedatives, amongst others, being used. Efficacy was rarely reported with exception of the use of some benzodiazepines and atypical antipsychotics, as well as the antihistamine hydroxyzinum in one case.

Mood disturbance figured prominently in 75 papers with several agents used from varying pharmacological groups but again with rarely reported efficacy. There were positive reports of the use of mirtazapine and some SSRIs, however this must be viewed with caution given the inclusion of a review paper that suggested that anti-depressant usage in prion disease is rarely beneficial symptomatically and appears associated with more rapid deterioration. In particular compared to first-generation antidepressants, the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) remained independently associated with significantly shorter survival time in sCJD patients with depression[46].

Catatonia was described in 7 papers with no consistent positive effects described but treatment most frequently attempted with high dose benzodiazepines.

Altered sleep behaviours or patterns including insomnia and parasomnias were mentioned in 52 papers. A broad selection of agents were described – many with efficacy – but these results should be interpreted with caution given the majority came from a single case report of a gentleman with Fatal Familial Insomnia and his experience of trialling multiple agents, often at high dose and in combination[47].

Cognitive impairment including disorientation, confusion, altered memory and attention span was frequently described and was reported in 78 papers. Small numbers of papers reported use of Donepezil and Memantine with no appreciable benefit reported. Flupirtine, in a small randomised control trial, seemed to improve memory and orientation when compared to placebo, but had no effect on language skills[48]. It should be noted this trial was undertaken to look for evidence of altered survival with flupirtine treatment, which was not shown, but has been included here as, although an attempt to treat the underlying pathology, it reported a symptomatic impact.

Psychosis including hallucinations, delusions and paranoia was described in 60 papers with a variety of anti-psychotics and benzodiazepines trialled. There were minimal positive reports of efficacy apart from single reports of rivastigmine, and combined donepezil and midazolam improving hallucinations. There were several reports of side effects thought to be secondary to pharmacotherapy, the majority being movement disorders.

Finally, there were reports of pharmacotherapy for management of behaviour such as aggression, often in the context of a constellation of neuro-psychiatric symptoms, described in 14 papers – with some positive reported effects in the use of a variety of atypical antipsychotics and benzodiazepines. Although management of altered or aggressive behaviours is key in managing patients such as these, the lack of clear descriptors in these papers limits our ability to draw definitive conclusions.

Summary of results for Pharmacological Management of Motor Symptoms

30 studies were identified for review regarding pharmacological management of motor symptoms. The selection process and an overview of the main characteristics of the included studies can be seen in the PRISMA diagram in figure 2, and supplementary table 3.

Fig 2. PRISMA diagram - Pharmacological Management of Motor Symptoms

Supplementary Table 3: Included Papers in Pharmacological Management of Motor Symptoms (grouped by study design)

Based on review of the included papers, descriptions were extracted of pharmacological management of motor symptoms. Efficacy was reported where there was any commentary made about improvement in symptom intensity or frequency. These were broadly subjective statements with no quantification available. Details of the descriptions extracted can be seen in supplementary table 4.

Supplementary Table 4: Reported Pharmacological Management of Motor Symptoms.

Again, much useful data is missing. The data broadly showed a small number of descriptions of positive symptomatic improvement, with the majority describing mixed reports and a number showing no positive effect. Many papers failed to detail the impact of the pharmacotherapy at all. Most papers lacked the full details of prescribing required to fully interrogate efficacy or potential lack thereof, with many missing details of dose, route, or efficacy. Several fail to clearly describe or delineate the indication for pharmacotherapies that could be employed in multiple scenarios e.g. benzodiazepines in the management of myoclonus or seizures increasing the risk of misinterpretation.

Myoclonus was the most frequently described motor symptom, described in 25 studies reviewed with 10 describing use of clonazepam, though with few reports of dosage and no reports of route or side effects. 3 papers reported on purported efficacy of clonazepam with 1 describing successful resolution of myoclonus, 1 describing reduction in frequency and 1 reporting no impact. 13 papers described use of sodium valproate though with minimal details offered, and only 4 offered a description of efficacy with 1 suggesting a worsening of myoclonus, 1 describing no effect and 1 describing some improvement in the myoclonus. 4 papers described use of levetiracetam with mixed effect. Drugs such as baclofen, phenytoin and diazepam were also mentioned in single publications but with scanty detail.

A single paper described use of haloperidol in chorea with some effect. Parkinsonism was treated with either dopa agents or selegiline with some positive reports, but use of rivastigmine and ropinirole seemed to have no positive effect.

Dystonia was described in 11 publications but pharmacological treatments including sodium valproate, phenytoin and clonazepam, described in single cases, were largely ineffective. Haloperidol did have some described efficacy. 1 publication described use of procyclidine, memantine and amantadine but with no report of any effect. In cases of spasticity both botulinum toxin and baclofen were used with some reports of efficacy for both. Ataxia was described in 12 papers, but no pharmacological treatments proposed.

Seizures were described in 14 papers but there was insufficient detail to delineate these into seizure subtypes. In many cases seizure activity was described as hard to treat with multiple lines of anticonvulsant drugs trialled without satisfactory effect. Only benzodiazepines, barbiturates and in some cases levetiracetam offered any reports of effective control of seizure activity.

Expert Opinion

Given a lack of published evidence and specific guidance, there was a desire to understand current practice based on expert opinion. Management of symptomatic individuals across the world varies significantly with different strategies being employed. For example, some groups involved in caring for patients with prion diseases are more interventional in aspects of management, for example, the use of early clinically assisted feeding routes (PEG or RIG for example) and even tracheostomy in some cases[49,50].

We designed a structured e-survey with inter-disciplinary input from members of the UK National CJD Research and Surveillance Unit (NCJDRSU) and Palliative Medicine experts across the UK. This was then distributed to members of the International CJD Surveillance Network and clinical teams who had made referrals to the UK National CJD Research and Surveillance Unit (NCJDRSU) to evaluate current practice regarding pharmacological management of symptoms in CJD.

Respondents were asked the frequency with which they saw each symptom, how troublesome they rated them to be and how effective pharmacological treatments were in providing control. They were also asked to list drugs they used including routes, doses, side effects and effectiveness.

Data was provided by 38 experts in 11 countries including neurologists, physicians, geriatricians, palliative care physicians, and nurses. The small numbers argue against more detailed analysis or comparison, but several themes emerged from responses some of which resonate with the findings from the published literature described above and some lacking that evidence base. A summary of the findings is demonstrated by the graph shown in figure 3, and included:

1. Neuropsychiatric Symptoms: These symptoms were generally considered more troublesome to manage, highlighting the significant challenge they pose in clinical settings.
2. Challenges of treatment: Ataxia and sleep disturbances were reported to be the least amenable to treatment.
3. Levetiracetam Use: There was widespread adoption of levetiracetam for managing myoclonus. Experts noted its good tolerability, ease of titration, and availability in multiple administration forms.
4. Anticholinesterase Inhibitors: These were increasingly used for managing visual hallucinations, with reports of good tolerance among patients.
5. Anti-psychotics and Benzodiazepines: These medications were commonly used for both neuropsychiatric and motor symptoms. While often effective, managing the balance of sedation presented a significant challenge.
6. No controversial or clearly divergent views were elicited.

Fig 3. Clinician experiences of CJD Symptoms reported in Online Survey

Discussion:

This scoping review describes the varied pharmacological approaches used to manage neuropsychiatric and motor symptoms associated with prion diseases. The review collates the evidence base for symptom management to 2022.

There has been a strong focus on diagnostics in CJD given the inherent difficulty outside of neuropathological study, but advances in CSF analysis with the RT-QuIC technique (Real-Time Quaking-Induced Conversion, a highly sensitive assay for prion detection)[51], has made inroads in improving diagnostic accuracy in-life. We are now in a position whereby we can start to focus on how we manage these individuals and provide evidence-based care for what is a devastating disease.

Details on the efficacy of pharmacological management remains inconsistent, with many studies reporting mixed results. Additionally, none of the papers used an objective score or marker to measure efficacy in symptom control where it was reported, and thus the incremental gain to the patient was unclear and subjectively described. Additionally, it is challenging to interpret the results in the context of insufficient detail and inconsistent reporting of co-prescribed drugs.

There does appear, however, to be some patterns emerging in reported practice despite uncertainty in the evidence base around drug classes that are routinely used.

- In the management of motor symptoms, drugs such as benzodiazepines, anti-psychotics and anti-epileptic drugs are used with some reports of effectiveness. There is insufficient evidence to offer guidance around dosage and route of administration.
- In the management of neuropsychiatric symptoms, drugs such as benzodiazepines and atypical anti-psychotics are used widely with some effectiveness described, mostly where sedation has a positive impact on symptoms. A range of drugs are used and there is insufficient evidence to offer guidance around dosage and route of administration.
- SNRIs should be used with caution in the management of mood disturbance given the suggestion that they may hasten disease progression and even shorten survival.

Benzodiazepines, anti-psychotic and anti-convulsant drugs are likely to be useful to clinicians caring for this cohort as they are widely available, commonly used in both neurological and palliative care practice, and are commonly used via subcutaneous route which is standard in most end-of-life care practice internationally. There may be a role for cholinesterase inhibitors for visual hallucinations. Palliative care practitioners may be less familiar with this class of drugs, needing support from physicians who routinely use these in practice.

Practice described above may be an example of extrapolation from the management of other neurodegenerative diseases with similar symptoms. Research is needed to understand whether different underlying pathologies require different therapeutic approaches.

This review includes data almost exclusively collated from case series, case studies and expert opinion. While useful to start to build a picture of practice, evidence is of low quality (level 4/grade C) and does not provide a robust evidence base [52]. The review process used a number of independent reviewers and synthesis software to try to minimise bias. However, the risk remains that papers which lack clarity in practice may be read with bias[53].

Prospective research is urgently needed to consider development of symptom assessment tools and to investigate pharmacotherapeutic strategies to manage motor symptoms and neuropsychiatric symptoms in prion diseases.

The protocol for this study is available, alongside all data extracted on request to the lead author.

Conclusion

For such a rare and challenging disease group as prion diseases we believe that enabling clinicians to categorise and assess symptoms well, and creating a platform for therapeutic randomised controlled trials focusing on symptomatic care is vital.

Currently there is clearly a lack of high-quality evidence to guide practice around caring for patients suffering from and dying of prion diseases. This risks poor quality care at the end of life with resultant suffering and distress to patients, families and staff. The imperative for additional clarity around symptomatic management is vital and trials of pharmacotherapy would be welcomed given the current position of equipoise. Without this we will never be able to make inroads into ensuring that this cohort of patients has equitable access to high quality palliative and end of life care, and well controlled symptoms.

We therefore suggest future research should focus on:

1. Standardised studies - there is a critical need for well-designed population-based studies that standardise dosages, route of administration and treatment regimens to provide clearer evidence on the efficacy and safety of pharmacological treatments in prion disease.
2. Innovative Therapeutic Approaches – to consider the role of novel therapeutic agents specifically for managing symptoms in prion disease.
3. Longitudinal Studies - Studies reporting the long-term use and efficacy of medications for symptom control are important to feedback quality of effect over time, side effects and any impact on disease process.
4. Patient-Centred Outcomes – Studies which report effect on patient or proxy quality of life reported outcomes can offer benefit in aligning goals of care with efficacy.

We will convene a Delphi study to synthesise clinical recommendations for symptom management in patients dying from prion disease.

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Conflict of Interest

The authors have no competing interests to declare.

Contributorship

The original review question and search strategy was developed and conducted by Dr John Centola.
Abstract and full text screening was conducted by Dr John Centola, Dr Anna Grundy, Dr Francesca Mastaglio, Dr Roseanagh Hogg, and Dr Victoria Bradley.
Data Extraction and thematic synthesis conducted by Dr Victoria Bradley and Dr Roseanagh Hogg.
Case vignettes written by Dr Eugene Ace McDermott and Terri Awe.

Patient and relatives' feedback was obtained and compiled by Terri Awe.
Expert opinion was gathered by an online survey designed, distributed, and analysed by Dr John Centola.
Scoping review drafted by Dr Victoria Bradley and Dr Roseanagh Hogg.
Paper reviewed and edited by Dr Suvanker Pal, Dr Mary Miller, Dr Matthew Carey, Dr Tomasz Bajorek, Dr Rachel Quibell and Dr Chloe Chin in addition to the other authors listed above.
All authors are part of a group currently working towards developing an evidence base and clinical guideline for symptom management in prion diseases.

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Figures

Fig 1. PRISMA diagram – Pharmacological Management of Neuropsychiatric symptom

Fig 2. PRISMA diagram -Pharmacological Management of Motor Symptoms

Fig 3. Clinician experiences of CJD Symptoms reported in Online Survey

Supplementary Material

Supplementary Table 1: Included Papers in Review of Pharmacological Management of Neuropsychiatric Symptoms (grouped by study design).

Supplementary Table 2: Reported Pharmacological Management of Neuropsychiatric Symptoms.

Supplementary Table 3: Included Papers in Pharmacological Management of Motor Symptoms (grouped by study design).

Supplementary Table 4: Reported Pharmacological Management of Motor Symptoms.