Pathophysiology and treatment of non-motor dysfunction in Amyotrophic Lateral Sclerosis

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Abstract:

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease typically presenting with bulbar or limb weakness. There is increasing evidence that ALS is a multisystem disease with early and frequent impacts on cognition, behaviour, sleep, pain and fatigue. Dysfunction of normal physiological and metabolic processes also appear common. Evidence from pre-symptomatic studies and large epidemiological cohorts examining risk factors for the future development of ALS have reported a high prevalence of changes in behaviour and mental health before the emergence of motor weakness. This suggests that changes beyond the motor system are underway at an early stage with dysfunction across brain networks regulating a variety of cognitive, behaviour and other homeostatic processes. The full impact of non-motor dysfunction continues to be established but there is now sufficient evidence that the presence of non-motor symptoms impacts overall survival in ALS and with up to 80% reporting non-motor symptoms there is an urgent need to develop more robust therapeutic approaches. This review provides a contemporary overview of the pathobiology of non-motor dysfunction, offering readers a practical approach with regards to assessment and management. We review the current evidence for pharmacological and non-pharmacological treatment of non-motor dysfunction in ALS and highlight the need to further integrate non-motor dysfunction as an important outcome measure for future clinical trial design.

Key points:

- ALS is a multisystem disease with 80% of patients reporting at least one non-motor symptom.
- Psychiatric, cognitive and behavioural symptoms are most common, though problems with sleep, autonomic function, pain and metabolism are increasingly recognised.

- Many of these symptoms are associated with shorter survival times and reduced quality of life.
- Over 35 clinical trials have been completed targeting non-motor symptoms in ALS however many are small, lack placebo arms, or are unblinded.
- A more concerted effort is needed to develop measures of non-motor dysfunction in ALS along with larger and more robust clinical trials.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative condition typically heralded by the onset of limb or bulbar weakness. Neuronal loss leads to progressive motor weakness, cognitive and behavioural disturbance, respiratory dysfunction and death. Most cases occur sporadically around the age of 60 with men affected more frequently than women [1]. Autosomal dominant mutations explain 10-15% of cases in European populations, with mutations in the chromosome 9 open reading frame 72 (*C9orf72)* gene most common [2]. ALS is neuropathologically characterised by a loss of motor neurons in the primary motor cortex and spinal cord, though increasingly is recognised as a multisystem disorder with degeneration beyond the motor system (Figure 1 & 2) [3,4]. Multiple lines of evidence suggest that neurodegenerative diseases target large-scale distributed brain networks early in the disease [5], and it may be that dysfunction across these structural and functional networks underpins many of the non-motor symptoms experienced by patients (Figure 3). With a 69% increase in the prevalence of ALS forecast by 2040 [6], there is an urgent need to develop new treatments to improve both survival and quality of life for patients. This review aims to

present the pathophysiological evidence for non-motor dysfunction in ALS and an overview of the current evidence base for the treatment of these problems.

2. Methods

2.1 Selecting non-motor symptoms

Deciding on the non-motor symptoms to include in the search was based on two factors. First, a clinical consensus meeting was held between authors to discuss the concept of non-motor symptoms and their occurrence within the ALS clinic and generate a list of potential symptoms based on combined clinical experience. Second, one author (CJM) held face to face interviews with a sample patient cohort (n=10). Open-ended questions regarding symptoms were presented to patients and responses were audio-recorded, transcribed and underwent linguistic analysis to identify common themes. This was then presented to a clinical expert group for final adjudication which resulted in the identification of six major domains: psychiatric, cognition, sleep, autonomic function, pain/fatigue and metabolism. These formed the basis for the subsequent literature search. A further two areas, sensory disturbance and olfaction were considered as exploratory non-motor symptoms based on the clinical experience of the authors. To validate the presence of these non-motor symptoms a standardised 28-question non-motor symptom questionnaire was created with patients/carers able to rate severity using a Likert scale.

2.2 Search strategy

A comprehensive search of MEDLINE for papers published in English between Jan 1, 1966, and December 31st 2020 was carried out, using the search terms "amyotrophic lateral sclerosis", "motor neuron disease", "ALS" and "Frontotemporal Dementia" in combination with "non-motor", "extra motor", "psychiatric", "cognition", "behaviour", "pseudobulbar",

"sleep", "pain", "fatigue", "autonomic", "sialorrhea", "metabolism", "lipids", "bone" "glucose" and also combined with "clinical trial". The final reference list was generated based on originality, study size, quality of the evidence, and its specific relevance to the diagnosis and management of non-motor symptoms in ALS. Emphasis was placed on more recent articles and clinical publications where possible, however, we did not exclude older publications if they were of significant importance.

3. ALS as a multisystem disease

3.1 A historical perspective

Whilst the canonical feature of ALS is motor weakness, with a final common pathway potentially being the degeneration of the motor system (see figure 1), there is significant neurobiological evidence that early degeneration of non-motor systems also occurs. This concept is not new with Charcot's student, Pierre Marie, documenting behavioural changes in advance of motor weakness a decade after Charcot's seminal description of ALS [7]. Since then various reports have followed; in 1961 patients in Guam presented with a triad of dementia, Parkinsonism, and ALS [8], whilst in the 1980s and 1990s more detailed clinicopathological reports linked ALS with cognitive and behavioural dysfunction [9,10].

A definitive molecular link between motor and non-motor symptoms was confirmed with the identification of a repeat expansion within the *C9orf72* gene [11] linking Frontotemporal Dementia (FTD) and ALS. This finding resulted in a paradigm shift in our understanding of the pathobiology of ALS, with the alternative peripheral 'dying back' hypothesis largely rejected, and ALS firmly considered a disease of the central nervous system [12]. Whilst the discovery of *C9orf72* has led to the identification of many shared pathological features across the spectrum of ALS and FTD [13,14], there remains significant phenotypic

variability: different sites of onset; different survival trajectories; and different degrees of non-motor dysfunction.

A possible explanation for this heterogeneity could relate to the presence of compensatory mechanisms, with adaptive responses regulated by an individual's genetics, neurodevelopment or exposure to environmental risks. This hypothesis is plausible given the substantial evidence that many neurodegenerative disorders target and spread through vulnerable large-scale brain networks [5,15] at an early stage, often prior to symptomatic onset, ultimately leading to neuronal death and brain atrophy. Early studies of brain volume in ALS failed to show consistent profiles of atrophy, however, advanced functional and microstructural neuroimaging studies now underscore the contemporary view of ALS as a multisystem disease, with evidence of more discrete targeting of both motor and non-motor networks [16]. As an example, there is consistent evidence of pathology within sub-cortical and highly interconnected hubs such as the thalamus [14,17].

3.2 Non-motor symptoms in advance of motor weakness

3.2.1 A clinical prodrome

In developing new multisystem models of ALS an important consideration is at what stage non-motor symptoms may manifest. There is growing evidence to suggest that a range of non-motor symptoms occur in advance of obvious motor weakness. Psychiatric illness has been reported in the pre-symptomatic period, occurring up to five years before the onset of motor symptoms [18], and additional population registry data has also suggested that those with preexisting psychiatric illness are 49% more likely to develop ALS [19]. Beyond this, there is an overrepresentation of psychiatric disease in first and second-degree family members of those with either both familial and sporadic ALS [20–22]. Hypermetabolism may manifest with a sharp reduction in body mass index (BMI) appreciable 10 years before clinical onset

[23], whilst elevations in lipids, particularly alterations apolipoprotein ratios, has been associated with a higher risk of developing ALS[24]. An important caveat to many studies suggesting a prodromal period of non-motor dysfunction is their retrospective nature. Furthermore, many of these symptoms are common in the general population, which poses a difficulty in ascribing a definitive clinicopathological link. To more robustly demonstrate a period of early non-motor dysfunction large prospective cohorts will be required. Whilst some data is provided from presymptomatic studies, the majority of ALS is sporadic making prospective observational studies challenging.

3.2.2 Evidence from presymptomatic studies

The idea that motor weakness may represent a late-stage event in the evolution of ALS is also supported by neuroimaging data. In presymptomatic familial ALS structural changes occur in the thalamus, dorsolateral prefrontal cortex [25–27], cerebellum [28], and white matter tracts including the anterior thalamic radiation, inferior longitudinal fasciculus and uncinate fasciculus first, with changes in the primary motor cortex and corticospinal tract occurring later [25,28,29]. Changes within functional networks are more complex with evidence of both reduced and increased connectivity across certain brain networks with one study of presymptomatic *C9orf72* carriers reporting reduced connectivity in salience and subcortical networks [26]. Another larger study found that whilst functional network connectivity is reduced in the presymptomatic period, network efficiency remains intact up until the point of symptom onset, suggesting that a potentially long period of compensatory activity occurs, before ultimately failing just prior to symptomatic onset [30]. Behavioural syndromes, particularly apathy or disinhibition [31–33], along with cognitive impairment in naming, executive function and praxis have been reported up to five years before expected onset in those with familial ALS [25,27].

3.3 Evidence of non-motor dysfunction following the onset of ALS

3.3.1 Neuroimaging studies

Whilst most neuroimaging studies have emphasised the involvement of the motor cortex [34] and corticospinal tracts [35], a comprehensive review of neuroimaging studies performed in ALS identified extra-motor atrophy in 21 of 26 studies, typically in frontotemporal and parietooccipital regions. White matter pathology involving the cingulum bundle, which serves a variety of executive and limbic functions, and also cerebellar white matter was reported in 25 out of 45 studies [36]. A more recent meta-analysis has also identified extra-motor structures, including the temporal pole, corpus callosum and superior longitudinal fasciculus, as being consistently involved in ALS [37,38]. In familial ALS associated with *C9orf72,* there are highly heterogeneous patterns of grey matter atrophy, though thalamic atrophy appears consistent [39,40]. In contrast, those with superoxide dismutase 1 (*SOD1)* mutations tend to have highly focal motor system involvement with the primary motor cortex and descending corticospinal tracts appearing solely involved [41].

Positron emission tomography (PET) imaging, typically using 18F-fluorodeoxyglucose, has shown widespread hypometabolism involving the frontal and prefrontal lobes, with hypometabolism correlating with the degree of cognitive impairment [42]. Several studies have also interestingly identified concomitant hypermetabolism in the cerebellum, brain stem and corticospinal tracts [43,44]. Task-free functional magnetic resonance imaging (MRI) has also demonstrated extra-motor dysfunction, though with more varied results when compared with structural and metabolic imaging [45]. Taken together, the most consistent findings suggestive of extra-motor dysfunction include reduced activation in sensorimotor [46], salience [47], and cortico-subcortical networks involving the basal ganglia [48], whilst increased activity is seen within cerebellar-subcortical networks [45,48]. The latter

finding is consistent with presymptomatic studies and provides support for the notion of either compensatory or topographically resilient networks maintaining normal function.

Less well studied are alterations in neurotransmitter profiles in ALS patients. However, the significance of any changes may be high given these neurochemicals underpin both local and long-range motor and non-motor functions. Proton magnetic resonance spectroscopy (1H-MRS) has been used to study glutamate in ALS, given its roles as a potentially excitotoxic agent, with an increased level in the motor cortex common [49]. Extra-motor glutamate is less well studied with only one study identifying increased levels in the pons [50]. In contrast reductions in other neurotransmitters appear common, albeit from relatively small studies, for example, gamma-aminobutyric acid (GABA) is reduced in the anterior and dorsolateral prefrontal cortices [51]; dopamine is reduced in the nucleus accumbens [52,53], and a 21% reduction in 5HT1a serotoninergic receptors has been identified in the cingulate and frontotemporal cortices [54].

3.3.2 Neuropathological studies

Several neuropathological studies have provided definitive evidence of extra-motor degeneration in ALS. An important caveat is that we can not yet image pathogenic protein spread *in vivo*, and therefore it creates uncertainty as to when extra-motor deposition of toxic species occurs. Notwithstanding this, several studies have identified neuropathological changes beyond the motor systems with cell loss and protein accumulation within frontal and temporal lobes, both limbic and extra-limbic [55–57]. Specific hallmarks of ALS such as bunina bodies have been identified in the cerebellum [58], whilst a study of 57 brains identified diffuse transactive repeat DNA binding protein 43 (TDP-43) deposition throughout the brain, with around three-quarters of patients having extra-motor involvement, most strikingly within the hippocampus and the cingulate cortex [59]. A more recent study confirmed and extended previous findings by identifying that the vast majority had TDP-43 pathology within

subcortical grey matter structures including the basal ganglia and thalamus [57]. Neuroinflammatory changes have also been identified in extra-motor regions with the presence of activated microglia in the dorsolateral prefrontal cortex, thalamus, and brain stem [60].

These widespread pathophysiological changes overlap with brain networks critical to normal cognitive, behavioural and other centrally mediated physiological processes. This substantial dysfunction therefore unsurprisingly results in a range of non-motor clinical problems which we discuss below.

4. Neuropsychiatric and cognitive dysfunction

4.1 Neuropsychiatric symptoms

Mental health-related symptoms are likely the most common non-motor symptom in ALS, though the prevalence rates are highly variable ranging from 1-75% depending on the screening methods used [61]. Although common, depression is typically mild for most, with moderate to severe depression in 10% of patients [62,63]. Though again there is variability in just how severe and persistent symptoms are with one large study reporting 17% met criteria for major depressive disorder, and 52% were prescribed anti-depressant medications [64]. Similarly, anxiety appears to have a varied prevalence, with estimates of moderate to severe anxiety in 19% to 50% of patients [65,66], most common in women and those with bulbar onset [67]. Of patients reporting anxiety, 43% will meet the criteria for agoraphobia, 33% for panic disorder [67], and 20% for generalised anxiety disorder [68]. Whilst suicide remains rare amongst ALS patients, 43% have reported suicidal ideation [69], and epidemiological data have suggested those with ALS are 6-times more likely to commit suicide, particularly in the first year after diagnosis [70].

The presence of psychosis in ALS is more likely in those with overlapping features of FTD, with one study reporting delusional beliefs in 50% compared to only 19% with FTD

alone [31]. The presence of *C9orf72* mutations as a cause of ALS-FTD appears critical in influencing psychiatric features, with one study reporting 65% of patients harbouring a mutation reporting psychotic features, compared to only 5% of those with sporadic disease [71].

An important consideration with regards to psychiatric symptoms is to what extent these are reactive or considered adjustment disorders in the face of what is a grave prognosis. Certainly, there is some evidence for this with anxiety peaking around the time of diagnosis and death, periods when worry surrounding aetiology and symptomatic burden are higher [68,72]. A further consideration is whether neuropsychiatric syndromes are driven by pathophysiological changes similar to those which underpin anxiety or depression in the normal population or if ALS-specific changes are occurring. This may have a bearing on both the prognosis, for example to what extent symptoms are reactive, as well as treatment strategies.

The neuropatholigcal substrate for primary mood disorders is likely different from that seen in ALS, with the former more likely to have cytoarchitectural abnormalities pertaining to neurodevelopmental abnormalities, whilst ALS is associated with protein accumulation and cell death [73]. Nevertheless both primary mood disorders and ALS target similar brain circuits, for example, areas of reduced brain volume in major depression disorder overlap with regions of greatest atrophy in ALS [74]. A further argument against a reactive process is that higher levels of depression, anxiety, and conditions such as bipolar disorder are reported in excess up to four years before the onset of ALS [18]. More recently a shared genetic basis between schizophrenia and ALS has been established [75], whilst unaffected family members of those harbouring a mutation in *C9orf92* are five times more likely to have schizophrenia or psychosis [20,21]. Finally, an emerging hypothesis relates to the possibility that pathological configurations of brain networks make individuals more vulnerable to both ALS and related

non-motor features, for example, there appears to be an increased risk of neurodevelopmental disorders such as autism in family members of *C9orf72* carriers [21].

4.2 Cognitive and behavioural disturbance

Estimates of cognitive impairment in ALS range from 20 to 50% [76,77] increasing in line with disease duration and motor severity [76,78]. Whilst impairment across most cognitive domains has been reported in ALS [79], executive dysfunction remains the canonical cognitive feature of ALS [77,80,81], with early reduction in verbal fluency, particularly letter fluency [82], and subsequent difficulties in planning and decision making [83]. Impaired performance on tasks of social cognition, such as interpretation of mental states of others and sarcasm perception, is also increasingly identified in ALS [83–86]. Language dysfunction beyond the problems of motor speech impairment is less well studied, however deficits in word retrieval and agrammatism have been reported, with loss of semantic knowledge also rarely occurring [87,88]. In one study 18% of patients with the non-fluent variant of Primary Progressive Aphasia went on to develop ALS, demonstrating how ALS may also present as a language-led disorder. Impaired episodic memory also occurs in ALS, with a large meta-analysis of 44 studies suggesting significant effect sizes on tests of delayed verbal and visual memory [79], although others have argued that these impairments may reflect working memory deficits [89]. Consistent reports suggest the neural substrate for deteriorating executive function includes degeneration of the dorsolateral and medial prefrontal cortices [42,90] whilst structural degeneration in the inferior frontal gyrus and superior longitudinal fasciculus has been linked to language impairment [91,92].

Behavioural symptoms may manifest before motor weakness [32], most commonly presenting with moderate to severe apathy in up to a third of patients, with disinhibition in around 20% [31,33]. Higher levels of behavioural disturbance have also been associated with reduced survival [93]. Up to half of patients will meet criteria for ALS with behavioural

impairment and a quarter will fulfil diagnostic criteria for FTD during their illness [78]. This may result from the accumulation of TDP-43 in Von Economo neurons within the anterior cingulate cortex, which are critical to normal social cognition [94]. Notably, behavioural disturbance can occur at all disease stages, though does increase in prevalence as motor weakness progresses [78]. Those with bulbar onset are more likely to develop behavioural disturbance compared to those with limb onset [95]. It has been suggested that those with 'upper-motor predominant' ALS are more likely to develop behavioural and cognitive impairment, however, a recent study casts some doubt on this with cognitive and behavioural disturbance detectable at similar levels irrespective of lower or upper motor neuron disease burden [96].

A related problem is that of pseudobulbar affect (PBA), characterised by heightened emotional lability [97], and present in 28-45% of patients [98,99], with more loosely defined criteria suggesting emotional lability occurs in 57% of patients [100]. As with other behavioural changes, PBA is more common in bulbar-onset ALS and occurs more frequently in upper-motor predominant disease and those with concomitant cognitive impairment [99,100].

4.3 Assessment of psychiatric, cognitive and behavioural symptoms

There are likely complex interactions in the genesis of psychiatric, cognitive and behavioural symptoms, for example, the presence of depressive symptoms are known to contribute to apathy [31,33], therefore patients should undergo assessment with complimentary tests across these domains. Formal neuropsychological assessment should be considered where possible. Ideally, measures validated in ALS populations should be utilised, examples of which include the Hospital Anxiety and Depression Scale [68] or ALS Depression Inventory [101]. Neuropsychiatric screening may include the informant completed Neuropsychiatric Inventory Questionnaire (NPI-Q) [102]. Widely available screening tools include the Edinburgh

Cognitive and Behavioural ALS Screen (ECAS) [103] and ALS Cognitive Behavioural Screen (ALS-CBS) [104]. Stand-alone cognitive and behavioural screening tools such as the Addenbrooke's Cognitive Examination III [105], the Frontal Systems Behaviour Scale [33], Dimensional Apathy Scale [106], the Beaumont Behavioural Index [107] and Motor Neuron Disease Behavioural Scale [93] have all been validated in ALS populations. As many cognitive tests can be impacted by motor weakness newer tests such as the Arrows and Colors Cognitive Test has been designed to allow assessment in those with severe motor weakness [108].

4.4 Management of psychiatric, cognitive and behavioural symptoms.

. An important point that cuts across all symptomatic domains is the importance of multidisciplinary team management, which has been shown to improve survival in its own right [109,110]. Neuropsychiatric symptoms in ALS may relate to the gravity of the diagnosis or the burden of physical symptoms [62,72,111], therefore, secondary causes should be identified and addressed in parallel to any specific psychiatric, cognitive or behavioural treatment. An overview of therapeutic trials is shown in table 1. A common approach in ALS is to use a single medication to manage multiple symptoms; amitriptyline, for example, helps with mood, secretion management, and pain. The average daily dose prescribed is 67mg, which may be insufficient to treat symptoms of depression [68], and frequent dose adjustments may be required to achieve efficacy. However, anticholinergic side effects such as cognitive impairment and urinary dysfunction may limit use. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used treatment for depression and remain the first-line treatment in ALS. Non-pharmacological interventions have included an eight week trial of meditation in 100 ALS patients, which showed improvements in quality of life with decreased anxiety and depression [112]; trials of cognitive behavioural therapy or music therapy have, however, shown no significant impact on depression or anxiety [113,114]. Most pharmaceutical trials targeting psychosis in neurodegeneration have targeted Alzheimer's

disease, however, one small study which included cases of FTD found that olanzapine, in doses ranging from 2.5mg to 10mg per day, was well tolerated and resulted in a significant reduction in delusions [115], although a larger trial failed to replicate this [116].

Across the ALS-FTD spectrum, SSRIs have been shown to improve behaviour, particularly disinhibition or agitation; citalopram, paroxetine, sertraline, and fluoxetine have all shown benefits suggesting a class effect [117]. Trazodone, which works as a serotonin antagonist and reuptake inhibitor, has also been trialled in a double-blind cross over study and was found to reduce neurobehavioural symptoms by more than 50% [118]. A recent study of 23 patients with FTD using up to 72 units of intranasal oxytocin twice daily showed modest improvements on tasks measuring social cognition and apathy after 7 days of treatment [119], with larger trials currently underway. SSRIs have traditionally been used off-label to manage PBA [97], however, in 2010 dextromethorphan/quinidine (marked as Neudexta) received Food and Drug Administration approval as the first specific therapy for PBA after clinical trials demonstrated a 50% reduction in daily episodes of emotional lability [120,121].

Currently, there is no evidence that any pharmacological therapy improves cognition in ALS. Cholinesterase inhibitors have been investigated for neuroprotective qualities in ALS without success [122], though only motor function was assessed [123]. In FTD cholinesterase inhibitors do not improve cognition and may worsen behaviour [124,125]. Memantine, an antagonist of glutamatergic neurons, has also been trialled in ALS without success, again with the caveat that effects on cognition were not assessed [126]. Non-pharmacological treatments, such as nocturnal non-invasive ventilation (NIV) has shown improvement in tests of immediate and delayed memory recall in one small trial [127].

5. Sleep disruption

Problems with maintaining normal sleep are twice as likely in those with ALS compared to healthy individuals [128]. The pathophysiology of sleep disruption is complex with symptoms of pain, respiratory failure, and mood, all likely contributing. More recently it has been suggested that degeneration within central sleep-regulating brain networks, which include brain regions preferentially impacted in ALS, such as the cingulate cortex and insula, also contribute to disrupted sleep [129]. Furthermore, the hypothalamus, a central component of sleep-wake regulation, shows particular vulnerability in ALS, with a 20% reduction in its volume reported [130].

Respiratory-related sleep disruption is probably the most commonly observed phenomena with sleep-disordered breathing occurring in 46%, whilst up to two-thirds of patients may have nocturnal hypoventilation [131,132]. However, other dyssomnias occurring in the absence of respiratory muscle weakness or sleep-disordered breathing are also common [128,132,133]: periodic limb movement of sleep occurs in 54% of patients [134]; restless leg syndrome is three times more likely in ALS [135], and loss of atonia during rapid eye movement (REM) sleep has also been reported in both sporadic [136] and familial ALS [137,138].

5.1 Assessment and management of sleep disturbance in ALS

Screening for sleep disturbance tends to focus on respiratory-related causes with tools such as the Epworth Sleepiness Scale [139] validated to detect obstructive sleep apnoea. Overnight pulse oximetry can also be used to identify nocturnal hypoxaemia, however, it can not detect the full range of sleep disorders. We would argue that given the incidence of other dyssomnias a more comprehensive approach to screening for sleep disorders should be used, with tools like the Sleep-50 questionnaire [140] or shorter Global Sleep Assessment Questionnaire [141] validated to detect up to six sleep-related disorders. These tools serve as

a broad tool to screen the general population and future studies are required to demonstrate their validity in the ALS population.

Management should first exclude secondary causes, such as pain, urinary incontinence, and sleep-disordered breathing. Recent drug changes should be reviewed, as both SSRIs and tricyclic antidepressants can cause sleep disturbance [142], and good sleep hygiene encouraged. An overview of therapeutic trials is shown in table 2. Melatonin, a hormone available without prescription in many jurisdictions is well-tolerated in ALS and has efficacy across the spectrum of sleep disorders [143]. Non-hypnotic benzodiazepine receptor agonists, such as zolpidem, appear safe in patients with severe hypercapnic airways disease, and can also be considered first-line [144]. In those with concomitant mood or behavioural disorders, trazodone may improve sleep efficacy [145]. One survey suggests that cannabis may be another option, though there are no trials to guide the selection of dosing or route of administration and some forms remain illegal [146]. Benzodiazepine use is cautioned due to the risk of worsening of respiratory function [144,147], though, one large meta-analysis reported no deterioration in those with sleep-disordered breathing [148]. Therefore, in the absence of significant overnight hypopneas, cautious use of benzodiazepines could be considered. In those with restless legs syndrome pregabalin or dopamine agonists are both licensed therapies. Overnight NIV is typically indicated in those with oxygen saturation of less than 88% for more than five minutes [131], however, it perhaps should be more broadly considered as it has been shown to improve sleep architecture irrespective of respiratory or bulbar involvement [149,150].

6. Autonomic dysfunction

Autonomic dysfunction is detectable in up to 75% of those with ALS, [151] likely resulting from a combination of degeneration within central structures, pre- or postganglionic nerves, or impaired neurotransmitter function. Central degeneration is supported by studies identifying degeneration within the intermediolateral nucleus, which conveys preganglionic

sympathetic nerves [152] as well as the rare clinical overlap between ALS and multiple systems atrophy, a central degenerative disorder characterised by autonomic failure [153]. Peripheral sympathetic hyperactivity is also plausible as a fivefold increase in levels of plasma noradrenaline has been reported in those with ALS [154].

The most commonly experienced symptoms include urinary urgency and frequency in 40% of patients [155,156] and gastrointestinal dysfunction, most typically constipation, in 50% [157]. More significant urinary incontinence has occurred in a third of patients and likely has multifactorial aetiology, with those over 60 or with increased spasticity more likely to have symptoms [157]. Urodynamic studies typically reveal a neurogenic bladder resulting from detrusor sphincter dyssynergia, and increased post-void residual bladder volumes in those with greater lower limb spasticity, implicating supra-sacral pathology [156,158]. Significant gastrointestinal symptoms such as faecal incontinence are less commonly reported in around 9% of patients [157]. Autonomic dysfunction may contribute to gastrointestinal issues, with one study of ALS patients identifying a significant proportion with delayed gastric emptying and prolonged colonic transit times [159].

Problems with control of oral secretion are common with 46% of patients reporting poor control [160]. Whilst most likely results from reduced oral clearance, reduced uptake of ^{99m}Technetium-pertechnetate in salivary glands suggests there is also changes to autonomic innervation which could contribute to increased production of thin secretions [161].

Although less conspicuous to patients, cardiovagal abnormalities, including reduced heart rate variability, are present in 50% of patients [151,162], though more serious cardiovascular autonomic failure appears rare [151,163]. However, patients with advancing disease may have exaggerated reflex tachycardia, hypertension and unexpected hypotension [163,164], with loss of parasympathetic control coupled with sympathetic hyperactivity resulting in circulatory collapse and rarely sudden death [163,165]. Excessive sweating is

common early on, possibly reflecting initial sympathetic overactivity, though this switches to reduced sweating in later disease [166].

6.1 Assessment of autonomic dysfunction

Autonomic symptoms are likely under-reported by patients and the use of dedicated clinical screening tools may increase detection. At present no screening tools have been validated in ALS. Pragmatic assessments include measurement of postural blood pressure and heart rates, routine urinalysis and measurement of post-void residual bladder volumes. Gastric emptying studies may be indicated in those with refractory gastrointestinal symptoms. An important consideration in the management of autonomic dysfunction is concomitant medications, with anticholinergic medications commonly contributing to symptoms [157]. Potentially useful tools for future validation could include the COMPASS 31, which is a brief but comprehensive screening tool assessing autonomic symptom severity across domains including bladder, gastrointestinal and cardiovascular function [167].

6.2 Management of autonomic dysfunction

Only one small placebo-controlled study has attempted to treat autonomic symptoms in ALS using intrathecal brain-derived neurotrophic factor, though this failed to show benefit [168]. Management of urinary symptoms may depend on bladder post-void residual volume and in those with large (>100ml) residual volumes the use of anticholinergic medication or intravesical botulinum may be helpful [169], or in some catheterisation may be required. Management of constipation should focus on increasing fluid and fibre intake, with an appropriate laxative regime if dietary modification is ineffective. In those with delayed gastric emptying prokinetic medications, such as metoclopramide [170] or domperidone [163] have been shown to improve symptoms.

Management of excess saliva can be particularly challenging due to variations in secretion viscosity and volume. Anticholinergic medications such as amitriptyline are helpful

in the management of thin secretions with 70% of patients reporting good control at doses of 25-50mg per day, though up to 100mg may be required [171]; alternatively, nebulised glycopyrrolate dosed at 1mg three times daily resulted in a 40% improvement [172], with the additional benefit of fewer cognitive side effects as it does not cross the blood-brain barrier [173]. Transdermal scopolamine can also be utilised with one trial showing a trend towards reduced suctioning requirements [174]. In a clinical trials of botulinum toxin, 82% of participants reported an improvement in secretions at 2 weeks, maintained for 12 weeks in 50% [175,176]. However, several different regimes and formulations have been used with only one head to head trial of botulinum type A and type B showing similar efficacy, though type B did have a shorter time to onset [177]. A recent pivotal phase 3 trial of rimabotulinumtoxin B also confirmed its benefit [178]. In ultra-refractory cases focused radiotherapy to submandibular and parotid glands has also been effective, though may take up to 2 months to work with up to 40% experiencing excessively dry mouth [179,180]. Thick secretions may respond to mucolytics such as pineapple juice, guaifenesin [181] and effervescent acetylcysteine [182], escalating to nebulized hypertonic saline [183] or mechanical therapies such as cough assist devices or portable suction.

7. Pain and fatigue

7.1 Pain in ALS

Pain is unsurprisingly common in ALS and is routinely reported by 75% of patients, most believing it to occurs as a direct result of their ALS [184]. The genesis of pain is likely multifactorial, resulting from combinations of nociceptive pain due to mechanical stress as well as dysfunction within somatosensory pain networks leading to central sensitisation [185]. This is supported by a study of *C9orf72* patients whose increasing pain correlated with atrophy of the posterior thalamus, though few others have examined the neural correlates of pain in ALS

[186]. Changes within somatosensory networks may also explain complaints such as itch, tingling or burning which occur in up to a third of patients [187]. Discomfort and pain from muscle spasms, cramps, and fasciculations are also common, particularly in those with limb-onset ALS, and are of moderate to severe intensity in over 50% [188].

7.2 Fatigue in ALS

In addition to this debilitating fatigue emerges in 80% of patients [189] and has been associated with faster disease progression [111]. Fatigue, like pain, is multifactorial and may relate to musculoskeletal and respiratory muscle weakness, and though it co-occurs with depression, it appears to be more common in those without depression [111]. Both physical and generalised fatigue occurs at similar levels, with the latter being more associated with motivation and psychological factors [190]. With apathy now recognised as a frequent behavioural symptom, future studies will be needed to identify to what extent this interacts with fatigue. There is direct physiological evidence to support why patients may experience physical fatigue, with impaired muscle contractility correlating with higher self-reported fatigue [191]. Levels of fatigue do not appear to correlate directly with motor weakness [192] or the degree of upper or lower motor neuron degeneration [193], underscoring its complex aetiology.

7.3 Assessment of pain and fatigue

Only 20% of ALS clinics routinely screen for pain or fatigue, likely resulting in underestimates of prevalence [187]. Simple assessments for pain include The Brief Pain Inventory which screens for location, severity, and impact [194] and has been used in ALS clinic populations [195]. The Multidimensional Fatigue Inventory (MFI) measures general fatigue, mental fatigue and activity-dependent fatigue [196] and has been correlated with poorer quality of life in ALS patients [190]. Physical fatigue can also be measured quantitatively using maximal force generation during sustained isometric muscle contraction

[197]. Working with members of the multidisciplinary clinic factors which may lead to pain and fatigue should be identified such as depression [185,190], respiratory failure [198], seating position and support at weakened joints.

7.4 Management of pain and fatigue

An overview of therapeutic trials for pain and fatigues shown in table 3. A recent Cochrane review found a lack of high-quality evidence for pharmacological treatment of pain in ALS [199], with small studies suggesting simple analgesia can control pain in 55% of patients [200]. Neuropathic pain is relatively uncommon in ALS [195], though guidelines suggest using either 50-100mg of amitryptiline daily or 900-3600mg gabapentin daily if present [109], these medications may also counter central sensitisation. Pain-related to spasticity may improve with oral baclofen [187] or intrathecal therapy in refractory cases [201]. Alternatively, levetiracetam at doses of 1500-3000mg daily has been trialled and found to improve spasticity related pain [202]. Opiate use in ALS is common and reported by 22% of patients [184], though the risk of respiratory depression limits use [203]. However, in advanced disease where respiratory distress and pain often co-exist, supervised use of opiates is recommended [109]. Cannabis is also increasingly considered by patients with one small study reporting an 80% improvement in pain control [204]. A recent larger study using a self-titrating regime of nabiximols found significant improvements in pain and spasticity compared to placebo [205].

Whilst cramp is a common cause of pain in ALS there have been few dedicated trials. Whilst magnesium is often recommended there is no evidence to suggest it is beneficial[204] A recent meta-analysis of all-cause cramp did suggest quinine sulphate reduced cramps by about a third [206]. Another meta-analysis of vitamin B complex and diltiazem failed to show benefit [207], as did a trial of tetrahydrocannabinol [208]. Open-label studies of levetericam and mexiletine for cramp have been conducted in ALS patients and did show significant

improvements in cramp frequency and severity [202,209]. Non-pharmacological approaches have also been trialled for pain in ALS, with case reports suggesting acupuncture may be beneficial [210], though a more rigorous placebo-controlled trial of osteopathy proved negative [211].

Pharmacological treatment for fatigue is generally not recommended unless particularly disabling [109], though an open-label study found fatigue severity reduced by 17%, and sleepiness reduced by 45% after two weeks of modafinal[212], and a small placebo-controlled study using 300mg of modafinil daily improved energy and stamina in 86% of patients [213], though 16% discontinued due to side effects. Drugs like amantadine and methylphenidate are sometimes also prescribed, however, a Cochrane review of therapies for fatigue in those with terminal illness only found weak support for amantadine in those with multiple sclerosis and no evidence to support use in other disorders [214]. Non-pharmacological studies have included resistance exercise programs and repetitive transcranial magnetic stimulation though neither reduced fatigue [215,216]. One recent study identified a trend towards worse fatigue in those treated with more intensive exercise regimens [217].

8. Metabolic dysfunction

ALS is increasingly seen as a hypermetabolic disorder, which has been suggested to be a homeostatic response compensating against loss of nerve and muscle fibres [3,218]. The exact mechanism underpinning altered body composition in ALS has not been established, and whilst reduced caloric intake is often hypothesised, this has not been borne out by studies showing those with ALS consume the same or more calories than age-matched controls [219]. It appears increasingly plausible that an increased metabolic rate may contribute to changes in body composition, with one study showing 41% of patients were hypermetabolic [220].

Hypermetabolic activity likely occurs early, supported by the fact that two-thirds of patients present with reduced BMI at diagnosis [221,222]. Body habitus is also an indicator of

future survival with the risk of death increased by 23% for every 10% loss from baseline weight [222]. Conversely, having an increased BMI has been linked with a lower lifetime risk of developing ALS, with risk decreasing as BMI increases [223]. Alterations in lipid metabolism also occur with a doubling of total cholesterol and low-density lipoprotein reported [224]. This may result from changes in cellular metabolism, reduced degradation of lipids or increased dietary preference for higher fat foods [219].

There is an ongoing debate as to the prevalence and causes of hyperlipidaemia in ALS, and whether or not hyperlipidaemia has a role in promoting or protecting against neurodegeneration [225]. These divergent views are reflected in studies showing a survival benefit of up to 14 months in those with hyperlipidaemia [224,226], whilst others report no such benefit [227]. Higher rates of impaired glucose tolerance and insulin resistance are also reported, possibly resulting from reduced ability to store glucose due to reduced muscle mass [228]. Whilst type-1 diabetes appears to increase the risk of ALS, there appears to be a lower incidence than expected in those with non-insulin-dependent diabetes [229]. This may relate to differences in pathophysiology, with one being an autoimmune condition, alternatively, it may relate to treatments given, for example, metformin has been posited as a neuroprotective therapy [230]. Bone health may also be impacted though there is a lack of large prospective studies in this area. However, two studies suggest a potential link with the presence of osteoporotic bone fractures associated with increased risk of later developing ALS [231], and low vitamin D levels at diagnosis associated with more severe motor weakness [232].

8.1 Assessment and management of metabolic dysfunction

Current guidelines recommend checking several metabolic biomarkers at diagnosis; including serum glucose, electrolytes, liver and bone function and creatine kinase [109]. More specific guidelines for managing metabolic health in ALS are currently lacking and a pragmatic

approach should involve monitoring of BMI, reviewing statin use, and monitoring bone health as dictated by local health policy. In those with low body mass index, one recent landmark clinical study showed that using a high-carbohydrate high-calorie diet, with total calories aimed at increasing weight by 0.5kg/week, was well tolerated and potentially associated with improved survival, though only 24 participants completed the study [233]. A subsequent observational study also found that long-term delivery of >1500 calories/day appeared to be associated with improved survival [234]. However, a recent study of a high caloric-fatty diet did not slow progression overall, though a post-hoc analysis of those with faster progression did suggest some benefit [235]. Percutaneous feeding has been shown to prolong survival in those with bulbar onset disease and should be considered if weight falls by 10% from premorbid levels or if oral intake becomes too difficult [109,236], although there remains a lack of high-quality randomised control trials directly comparing percutaneous with ongoing oral feeding regimes [237].

Statin use in ALS remains controversial, with one study suggesting they are protective [238], whilst others suggest they are a risk factor for both the development of ALS or more rapid functional decline [239] [240]. Until more definitive data is available our approach is to avoid their use for primary prevention in low-risk individuals following a diagnosis of ALS with careful monitoring for statin-related side effects in those who remain on them. Other areas such as bone health are less well studied. One small study which supplemented vitamin D resulted in a slower rate of decline in function, compared to standard treatment [241]. However data is conflicting with another study showing no benefit [242], and in another supplementation was associated with faster disease progression [232].

9. Other non-motor symptoms

Many other non-motor symptoms have been reported in addition to those previously mentioned and require more detailed discussion in future reviews, for example, extrapyramidal and cerebellar dysfunction. Parkinsonism was most notably linked to ALS with the description of cases from Guam, however, Parkinsonism may occur in between 5-15% of those with ALS, most typically manifesting with postural instability [243], with a more recent study identifying up to 30% of ALS patients having some extrapyramidal features [244]. Co-existing cerebellar ataxia appears less common in ALS, though the role of the cerebellum in the pathogenesis of ALS requires closer scrutiny given changes in metabolism seen on functional imaging [36] as well as the cerebellar pathology seen in *c9orf72* carriers [245]. Other sensory symptoms have also been reported, with impairments in olfaction twice more likely in ALS than healthy individuals [246], whilst others have shown evidence of sensory involvement [247], which may explain unusual variants of ALS such as facial onset sensory motor neuronopathy (FOSMN) [248].

10. Conclusions and future directions

This review provides a contemporary overview of the growing pathophysiological and therapeutic literature relating to non-motor dysfunction in ALS, which increasingly emphasises ALS as a multisystem disorder (see Figure 3). We have highlighted the current evidence-base for the assessment and management of symptoms across non-motor domains, whilst also providing pragmatic therapeutic approaches based on extensive clinical experience. A clear theme throughout this review has been that non-motor dysfunction contributes to a more rapid decline and a worse prognosis for those with ALS. Whilst we have provided data from over 35 interventional studies aimed at treating non-motor symptoms the majority of these have been small and not robustly designed. An important future goal should be the development of large

placebo-controlled clinical trials to rigorously assess the efficacy of therapies for non-motor dysfunction. A rationale for such trials is based on the fact that some non-motor symptoms are associated with shorter survival, therefore reducing their impact may prolong survival as well as improving quality of life. These future trials will require suitable outcome measures for non-motor symptoms to demonstrate efficacy. Such outcome measures should be able to track the broad range of non-motor symptoms longitudinally in a patient-centric manner, whilst also being efficient to administer. An example of such a screening tool, developed together with patients at our centre, is presented in Figure 4. This screening tool was administered to an initial local cohort of 35 participants who endorsed symptoms across all domains. Good levels of internal consistency were seen with this screening tool (Cronbach's alpha=0.844) though further large-scale and longitudinal validation will be required.

Whilst non-motor dysfunction in ALS is not a new concept, there is now growing evidence supporting the notion that non-motor dysfunction can occur in advance of motor weakness, in particular neuropsychiatric, behavioural and metabolic dysfunction [18,23,32]. Up to 80% of individuals experience some symptomatic non-motor dysfunction during their illness, with variable but overlapping clinical syndromes [61,76,151,189]. Evidence, particularly from presymptomatic studies, suggest that this heterogeneity may result from either the topographical organisation of key brain networks, their compensatory capacity, or lack thereof [26,27,30]. However, there remains a considerable lack of knowledge with regards to the evolution of non-motor symptoms in pre-symptomatic and prodromal stages, and as ALS is typically a sporadic disease collecting pre-symptomatic data has proven difficult. Future studies may be able to exploit the increased utilisation of centralised electronic health records to more robustly establish the extent and evolution of non-motor dysfunction prior to diagnosis. Alternatively, data from prospective biobanking studies, such as UK Biobank, may in the future provide further knowledge. Further insights into prodromal disease may also be provided by

exploring beyond the nervous system, for example, the immune and gastrointestinal systems have been implicated in a range of neurodegenerative disorders [249,250].

Figure 1 and 2 summarise the current knowledge regarding the broad profile of molecular dysfunction occurring in ALS as well as potential conduits for disease propagation. An important theoretical question continues to pertain to the mechanism by which ALS pathology propagates. One emerging mechanism is that of prion-like propagation, which has been demonstrated in both TDP43 and SOD1 proteinopathies [251]. Though normal SOD1 and TDP43 are expressed throughout the brain *SOD1* mutations result in a lower motor neuron predominant degeneration, which may be explained by a greater tropism for the anterior horn cell [252]. TDP43 appears to propagate in a more widespread fashion, with some arguing it spreads is corticofugal from the motor cortex and brain stem motor nuclei to frontotemporal and subcortical regions at a later stage [253]. This more widespread propagation of TDP43 is likely contributory to the greater range of non-motor dysfunction in this group and the purer motor phenotype seen in *SOD1* mutation carriers. However, further work is needed to establish the mechanism by which these proteins propagate and ultimately identifying the factors leading to these divergent presentations may have important therapeutic implications.

Future approaches in the classification of ALS may need to utilise a more systems-based approach in diagnosis and classification of disease severity, which may improve the accuracy of prognosis and guide more informed therapeutic decisions. This will likely require the collection and integration of multimodal biomarker datasets, providing a more precision-medicine approach to treating ALS, including the development of earlier and more targeted clinical trials.

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Author contributions.

CJM and MCK conceived this article. CJM, RMA, WH and MCK determined the scope of article. CJM undertook the literature search and completed the initial draft paper. RMA, WH, ST, JDR, RSB, OH provided critical commentary and revised the final article.

Therapy investigated	Study Design and duration	Subjects	Outcome	Year, reference
Neuropsychiatric				
Olanzapine 2.5-10mg daily	Case-control, 24 months	17*	Reduced delusions, emotional lability and irritability. Increased somnolence in 31%	Moretti, 2003, [115]
Trazodone 150-300mg daily vs. placebo	R, DB, PCT, 6 weeks	31	Significant reduction in neurobehavioural symptoms on trazodone	Lebert, 2004, [118]
Sertraline, Citalopram, Trazodone vs. placebo	Cochrane review	692**	Significant reduction in agitation with active treatments list compared to placebo	Seitz, 2011, [255]
Amitriptyline, SSRIs or Mirtazapine for depression	Guideline	NA	Good clinical practice point	Andersen, 2012 [256]
Bupropion, diazepam, sublingual lorazepam for anxiety	Guideline	NA	Good clinical practice point	Andersen, 2012, [256]
10 CBT sessions vs. usual care	R, SB, 10months	15	No improvement in depression, terminated early due to poor recruitment	van Groenestijn, 2015, [113]
Active music therapy vs. usual care	R, OL, 4 weeks	30	No improvement in anxiety or depression, improved QoL	Raglio, 2016, [114]
Meditation vs. usual care	R, OL, 12 months	100	Higher QoL scores, lower depression and anxiety scores with meditation	Pagnini, 2017, [112]
Cognition/Behaviour				
NIV	OL, 6 weeks	9	Improvement in list learning after NIV treatment	Newsom-Davies, 2001, [127]
Donepezil 10mg daily vs usual care	OL, 6 months	24*	No improvement in cognition, worsening of behaviour in those on donepezil	Mendez, 2007, [125]
Galantamine 8-12mg daily vs. placebo	OL, 18 weeks; R, DB, PCT ext 8 weeks	36*	No significant differences in behaviour or language detected	Kertesz, 2005, [124]
Dextromethorphan/quinidine 20/10mg twice daily vs. placebo	R, DB, PCT, 12 weeks	197	50% reduction in episodes of emotional lability in those on the active therapy	Pioro, 2010, [121]
Memantine 20mg daily vs. placebo	R, DB, PCT, 26 weeks	81*	No improvement in behaviour or cognition	Boxer, 2013, [257]
Oxytocin 24-72 IU twice daily vs. placebo	R, DB, PCT, 1 week	23*	Primary endpoint (safety/tolerability) met, trend toward improved empathy	Finger, 2015, [119]

Table 1: Overview of published therapeutic interventions for neuropsychiatric and cognitive symptoms in ALS ordered by symptoms and year of publication. R, randomised; DB, double-blind; PCT, placebo-controlled trial; SB, single-blind; OL, open-label; ext, extension phase; CBT, cognitive-behavioural therapy; QoL, quality-of-life; * patients with Frontotemporal Dementia, ** patients with dementia,

Therapy investigated	Study Design and duration	Subjects	Outcome	Non-motor symptom (year, ref.)
Sleep disturbance				
NIV	OL, 1-2 weeks	15	Improved oxygen saturations, no change to other sleep parameters	2013, [258]
NIV	OL, 1 month	24	Improved sleep architecture (slow-wave and REM) and reduced arousals after treatment	2015, [150]
Autonomic				
Botulinum toxin type A 75U vs. placebo	R, RB, PCT, 24 weeks	32	At 4 weeks 50% reduction in saliva volume in treatment group	2003, [176]
Intrathecal BDNF	DB, PCT, 9 months	10	No difference in autonomic parameters (e.g. sudomotor activity) after treatment	2005, [168]
Botulinum toxin type B 2500U vs. placebo	R, DB, PCT, 12 weeks	20	At week 2, 82% had improvement, by week 12 50% reported improvement.	2009, [175]
Amitriptyline, atropine drops, hyoscine	Guideline	NA	Good clinical practice point	2012, [256]
10 or 20 Gray radiation to salivary glands	Case-control, 6 months	50	65% had maintained a reduction in saliva at 6 months	2014, [180]
Scopolamine Patch	DB, PCT Cross-over, 4 weeks	10	No difference in saliva. Trend towards reduced suctioning	2018, [174]
RimabotulinumtoxinB 2500U or 3500U vs. placebo	R, DB, PCT, 4 weeks	187*	Significant reduction in saliva production up to 13 weeks	2020, [178]
Metabolism				
High carbohydrate, high-fat diet vs. standard care	R, DB, PCT, 5 months	24	Improved survival in high carbohydrate diet compared to standard care	2014, [233]
3 monthly assessment of BMI, Lipids and survival after PEG placement	OBS	89	After 12 months a survival benefit emerged in those receiving >1500 calories/day	2015, [230]
High caloric-fatty diet (405kcal/day) vs. standard care	R, DB, PCT, 18 months	201	No overall benefit. Faster progressors slowed progression	2020, [235]
Cholecalciferol 25,000-100,000 U/week, vs. standard care	OL, 6 months	48	No survival benefit with high dose vitamin D	2017, [260]
Vitamin D 50,000IU v 75,000 IU v 100,000IU monthly	OL, R, 6 months	33	No alteration of disease progression	2020 [242]

Table 2: Overview of published therapeutic interventions for sleep, autonomic and metabolic symptoms in ALS ordered by symptoms and year of publication. R, randomised; DB, double-blind; PCT, placebo-controlled trial; SB, single-blind; OBS, observational study' OL, open-label; NIV, non-invasive ventilation; BDNF, brain-derived neurotrophic factor; * 12 had ALS.

Therapy investigated	Study Design and duration	Subjects	Outcome	Year, ref
Pain				
Intrathecal baclofen	OL, 9 months	8	54% reduction in pain score at follow-up	2008, [201]
Levetiracetam 1500-3000mg daily	OL, 6 months	20	47% reduction in cramp severity score at follow-up	2009, [202]
THC vs. Placebo	R, DB, PCT, 8 weeks	27	No improvement in cramps on THC	2010, [208]
Gabapentin, pregabalin, amitriptyline for neuropathic pain	Guideline	NA	Good clinical practice point for neuropathic pain	2012, [256]
Quinine sulphate 250-500mg daily vs. Placebo	Cochrane review	1586^	Combined reduction in cramp frequency by 28% after two weeks	2015, [206]
Mexiletine 300-900mg daily vs. placebo	R, DB, PCT, 12 weeks	60	Cramp frequency reduced to 31% of the placebo frequency rate.	2016, [209]
Osteopathy vs. physiotherapy	R, SB, 12 weeks; OL ext, 10 weeks	14	No difference in QoL or pain scores at follow-up	2016 [211]
Magnesium (elemental) 200-802mg daily	Cochrane review	735^	No improvement in cramps	2020 [259]
Self-titrating up to maximum of 32.4mg delta-9-THC and 30 mg cannabidiol daily vs. placebo	R, DB, PCT, 13 weeks	59	Significant improvement on pain and spasticity scales	2019, [205]
Fatigue				
Daily Resistance exercise regime	R, vs. std care	27	No difference in fatigue. Improved QoL in exercise group	2007, [215]
Modafinil 100-300mg daily	R, DB, PCT, 4 weeks; OL ext, 8 weeks	32	76% on active therapy reported global improvement. Significant improvement in fatigue	2010, [213]
Modafinil 200mg or 400mg daily	OL, 2 weeks	15	17% reduction on fatigue severity scale. 45% reduction on Epworth Sleepiness Scale	2005, [212]
Intensive (50 sessions) vs. Usual (30 sessions) of exercise	R, SB, RCT, 18 months	65	Trend towards worse fatigue in intensive group	2019, [217]

Table 3: Overview of published therapeutic interventions for pain and fatigue s in ALS ordered by symptoms and year of publication. R, randomised; DB, double-blind; PCT, placebo-controlled trial; SB, single-blind; OL, open-label; ext, extension phase; QoL, quality-of-life; THC, tetrahydrocannabinol. ^ combined reporting of cramps due to any cause.

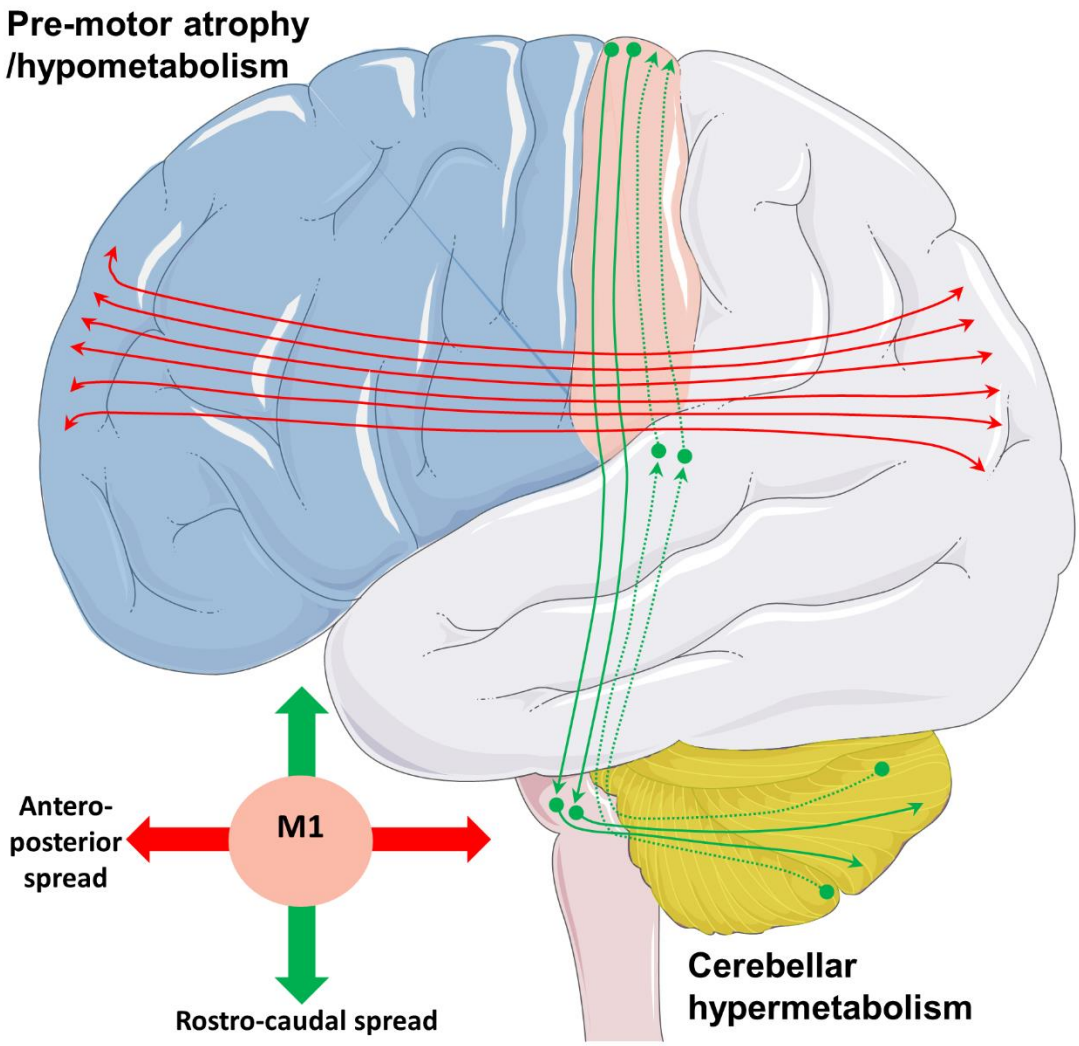

Figure 1. Structural evidence for non-motor system dysfunction in ALS. Prefrontal cortices regularly have excess brain atrophy or hypometabolism in those with ALS. Pathological brain network activity may also be influenced by hyperexcitability of some regions, with the cerebellum showing hypermetabolism on metabolic imaging. In ALS, the Primary Motor Cortex (M1) is pathognomically involved. However, its involvement across disease stages is unclear. Involvement of M1 may reflect the point of disease onset with spread to non-motor regions anterior-posteriorly, via association tracts such as superior longitudinal fasciculus (red solid line), or via rostrocaudal projections such as descending cortico-pontine-cerebellar fibres (green solid line). Alternatively early non-motor dysfunction may suggest disease spread from non-motor regions via ascending connections such as cerebello-thalamic-cortical fibres (green dashed lines) or other reciprocal connections between motor and non-motor structures.

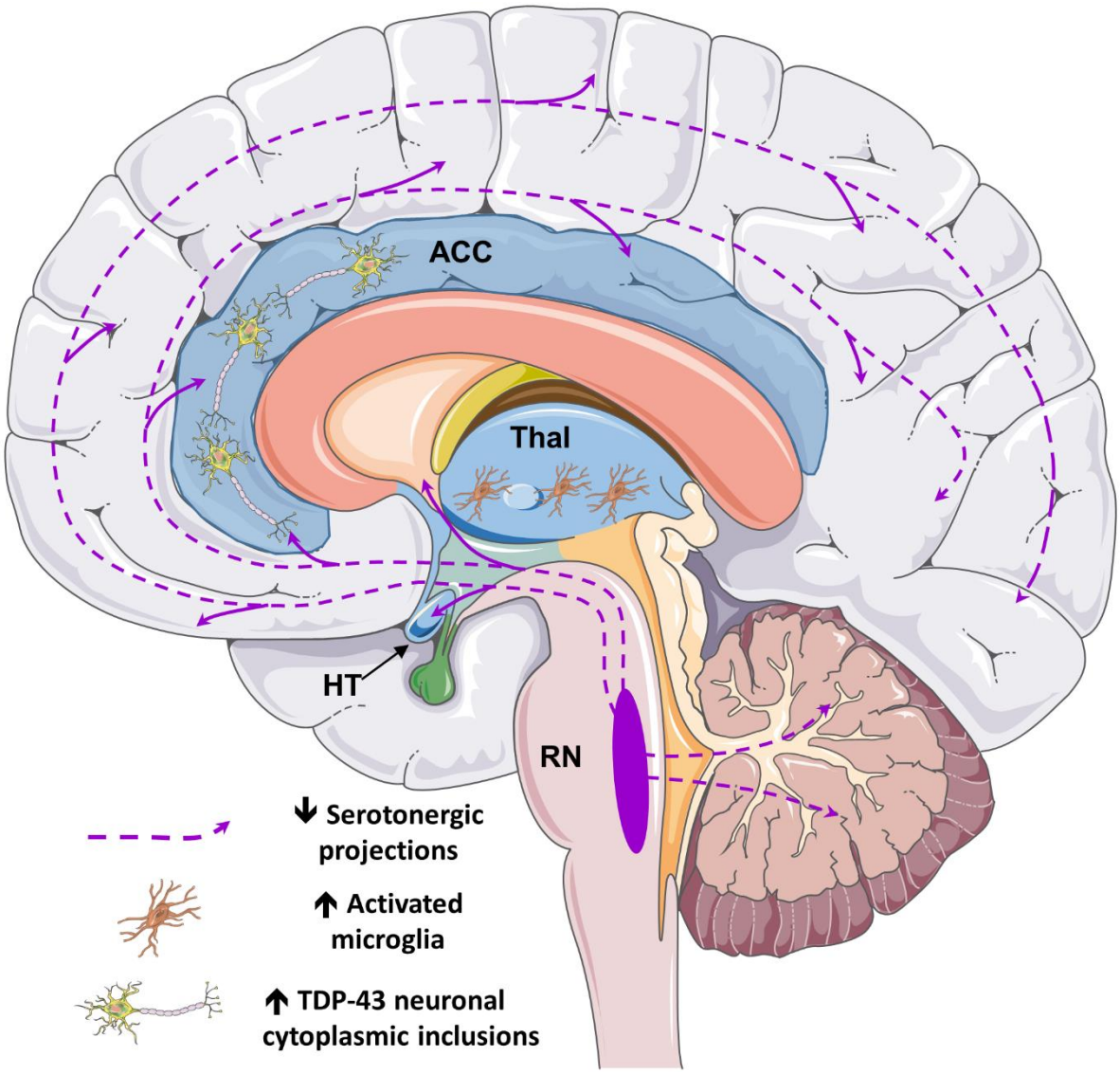

Figure 2. Subcortical, neurochemical and neuropathological evidence of non-motor dysfunction. ALS is increasingly recognised as a multisystem disorder. Pathological mechanisms such as loss of long-range projections, in this case, evidence by reduced serotonergic projections (dashed purple line) from the Raphe Nuclei (RN), may lead to many of the cognitive and neuropsychiatric features seen. Consistent evidence has also pointed to the involvement of the thalamus (Thal), and given its role as the brains major afferent and efferent relay station may facilitate disease propagation. More recently evidence has emerged implicating hypothalamic (HT) dysfunction in metabolic and autonomic dysfunction in ALS. Finally, neuropathologically changes are seen beyond the primary motor cortex with both the thalamus and anterior cingulate cortex (ACC) involved.

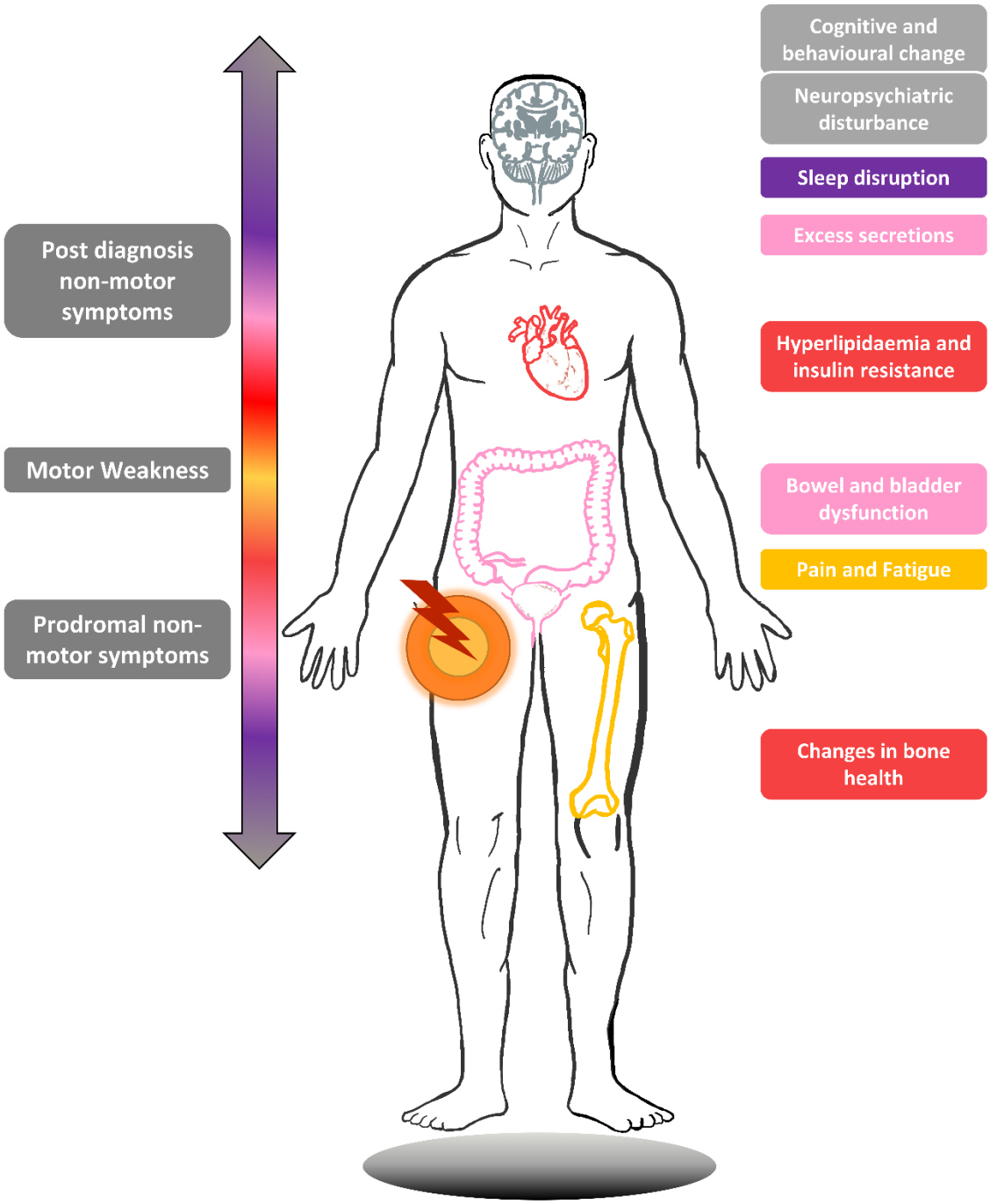

Figure 3. The spectrum of non-motor symptoms in ALS. The bi-directional coloured arrow reflects the fact that non-motor symptoms may occur in variable temporal order, and can occur prior to or after the onset of motor weakness. Non-motor domains are highlighted on the right. The coloured disc and lightening bolt signify pain and fatigue.

Questionnaire for Non-Motor Symptoms in ALS

Please Tick: Carer ☐ Patient ☐

Name: Date:

Thinking back over the last 3 months, read each statement and circle how often you have seen or experienced each issue as a change from normal in the patient/yourself. You may wish to consult with someone you know regarding some questions.

Rare = Once a month **Sometimes** = Less than weekly but more than once a month
Often = 1-4 times a week **Constant** = Daily

I have difficulty focusing and completing tasks	Never	Rare	Sometimes	Often	Constantly
I have difficulty finding the right word to say	Never	Rare	Sometimes	Often	Constantly
I don't always recognise when someone is upset	Never	Rare	Sometimes	Often	Constantly
I have less motivation to do new things	Never	Rare	Sometimes	Often	Constantly
I can be inappropriate around others	Never	Rare	Sometimes	Often	Constantly
I can laugh or cry for no particular reason	Never	Rare	Sometimes	Often	Constantly
I feel sad more often than happy	Never	Rare	Sometimes	Often	Constantly
I find it hard to take pleasure in things	Never	Rare	Sometimes	Often	Constantly
I feel tense or frightened	Never	Rare	Sometimes	Often	Constantly
I have strong beliefs that others find strange	Never	Rare	Sometimes	Often	Constantly
I have had hallucinations	Never	Rare	Sometimes	Often	Constantly
I have trouble falling or staying asleep	Never	Rare	Sometimes	Often	Constantly
I tend to snore loudly at night	Never	Rare	Sometimes	Often	Constantly
I jerk or thrash about in my sleep	Never	Rare	Sometimes	Often	Constantly
I feel so fatigued that I have to stop and rest	Never	Rare	Sometimes	Often	Constantly
It takes a lot of motivation to do things	Never	Rare	Sometimes	Often	Constantly
I have been bothered by pain	Never	Rare	Sometimes	Often	Constantly
I have been taking painkillers	Never	Rare	Sometimes	Often	Constantly
I have pain so bad that it stops me from doing tasks	Never	Rare	Sometimes	Often	Constantly
I have noticed a change in sweating	Never	Rare	Sometimes	Often	Constantly
I have had difficulty passing or controlling urine	Never	Rare	Sometimes	Often	Constantly
I have felt constipated	Never	Rare	Sometimes	Often	Constantly
I am bothered by too much saliva	Never	Rare	Sometimes	Often	Constantly
I have noticed a change in my sense of smell	Never	Rare	Sometimes	Often	Constantly
I have noticed tingling or numbness in my body	Never	Rare	Sometimes	Often	Constantly
I feel like I'm losing weight, without changes to my diet	Never	Rare	Sometimes	Often	Constantly
I perceive temperatures differently to other around me	Never	Rare	Sometimes	Often	Constantly
I have noticed a change in fat distribution on my body	Never	Rare	Sometimes	Often	Constantly

Figure 4. A proposed screening questionnaire for non-motor symptoms in ALS covering multiple domains, with question frequency and order based on the occurrence of non-motor symptoms. Patients are asked to rate frequency and each answer is coded from 0 (never) to 4 (constantly), provided a range from zero to a maximum of 112.

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