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Review article

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Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation

In the format provided by the authors and unedited

SUPPLEMENTARY TABLE 1: Currently available symptomatic and neuroprotective treatments for ALS

Grade A therapies where the evidence is based from systematic review or a randomised controlled trial with narrow confidence intervals are highlighted. Relevant references are appended.

SYMPTOMATIC THERAPIES	
Respiratory failure	Non-invasive ventilation (NIV) (**Grade A**)[1]; Cough assist device[2]; tracheostomy-ventilation used in some countries[3].
Dysphagia	Attention to food consistency and swallow technique; nutritional supplements; gastrostomy placement using one of several potential methods[4].
Dysarthria	Advice from Speech Therapist; voice banking[5]; a variety of communication aids including computer programmes controlled by eye gaze.
Oro-pharyngeal secretion management	**For excessive thick oro-pharyngeal secretions:** carbocisteine as a mucolytic agent; nebulised saline; humidification of NIV system; cough assist device; suction device; pineapple juice. **For excessive oral saliva (thin secretions**)[6]**:** hyoscine transdermal patches; amitriptyline; atropine orally or as sublingual drops; glycopyrrolate; intra-salivary gland botulinum toxin; suction device.
Dry mouth	Artificial saliva spray or gel; humidification of NIV.
Muscle cramps	Quinine sulphate[7]; levetiracetam[8]; mexiletine[9]; physical therapy.
Pain	WHO Analgesic ladder; non-steroidal anti-inflammatory agents (NSAIDs); amitriptyline; opioids; steroid injection for frozen shoulder.

Spasticity	Baclofen, tizanidine, dantrolene, benzodiapzepines; prescribed exercises[10].
Emotional lability	Serotonin reuptake inhibitors (SSRIs)[11]; amitriptyline[12]; combined dextromethorphan-quinidine (**Grade A**)[13].
Fatigue	Modafinil[14].
Mood alterations	Benzodiazepines for anxiety; SSRIs or tricyclic anti-depressants (TCADs) for depression; psychological therapy/counselling.
End of life care	Palliative care team involvement. Opiate or anxiolytic medications may be required to alleviate discomfort or distress.
DISEASE MODIFYING THERAPIES	
Riluzole	Riluzole (**Grade A)** inhibits glutamate release from pre-synaptic terminals, by inactivating voltage-dependent sodium channels and is considered to reduce motor neuron excitotoxicity. The original trial results indicated a modest improvement in survival by approximately 3 months[15], but a more recent assessment suggests that there may be a more substantial effect on life expectancy[16].
Edaravone	Edaravone (**Grade A**) is a free radical scavenger anti-oxidant administered IV for 14 successive days per month. It has been reported to delay the progression of disability over a 6 month time frame in a highly selected sub-group of ALS patients[17]. It has been approved for ALS treatment in Japan and the USA but not in Europe.

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Supplementary Table 2

Genes identified as causative or increasing the risk of ALS

ALS – amyotrophic lateral sclerosis; FTD – frontotemporal dementia. AD= autosomal dominant; AR= autosomal recessive. ALS-new represent newly described potential ALS genes that require further validation; ALS-putative represent potential genetic risk factors; FTD-ALS are genes known to be associated with both ALS and FTD. Relevant references are appended.

ALS Locus Number	**Gene**	**Encoded protein**	**Chromosomal location**	**Inheritance**	**Phenotypic features**	**Protein function:** **Disease mechanisms**	**Original references**
ALS1	*SOD1*	Cu-Zn superoxide dismutase	21q22.11	AD (AR)	Adult-onset, usually limb-onset. Not associated with dementia. Not a TDP-43 proteinopathy.	Dismutates superoxide free radicals: Oxidative stress; protein aggregation; mitochondrial dysfunction; axonal transport defects; proteasome impairment; glial dysfunction	Rosen et al, 1993[1]
ALS2	*ALS2*	Alsin	2q33.1	AR	Infantile and juvenile-onset, slowly progressive ALS mainly affecting upper motor neurons.	Intracellular trafficking.	Hadano et al., 2001[2]; Yang et al., 2001[3]
ALS4	*SETX*	Senataxin	9q34.13	AD	Juvenile-onset, slowly progressive ALS.	RNA processing.	Chen et al., 2004[4]
ALS5	*SPG11*	Spatacsin	15q21.1	AR	Juvenile-onset, slowly progressive ALS	Vesicle trafficking; axonal defects.	Orlacchio et al., 2010[5];

					mainly affecting upper motor neurons.		Chia et al.,2018[6]
ALS6	*FUS*	Fused in sarcoma RNA binding protein (component of the hnRNP complex)	16p11.2	AD (AR)	Large variation in the age of disease onset, but with a median younger than for sporadic ALS. Typical or atypical ALS and FTD[6].	RNA processing; DNA damage repair defects; nucleocytoplasmic transport defects; stress granule function; protein aggregation.	Kwiatkowski et al., 2009[7]; Vance et al., 2009[8]
ALS8	*VAPB*	Vesicle-associated membrane protein	20q13. 32	AD	Adult-onset, typical or atypical ALS.	Proteasome impairment; intracellular trafficking.	Nishimura et al., 2004[9]
ALS9	*ANG*	Angiogenin	14q11.2	AD	Adult-onset, typical ALS and FTD.	RNA processing.	Greenway et al., 2006[10]
ALS10	*TARDBP*	TAR DNA binding protein 34 (TDP-43)	1p36.22	AD	Adult-onset, typical ALS not associated with overt cognitive dysfunction. Limb or bulbar onset, considerable variation in age of onset and rapidity of disease course.	RNA processing; nucleocytoplasmic transport defects; stress granule function; protein aggregation.	Sreedharan et al., 2008[11]; Rutherford et al., 2008[12]
ALS11	*FIG4*	Polyphosphoinositide phosphatase	6q21	AD	Adult-onset, clinical variability with incomplete penetrance.	Intracellular trafficking.	Chow et al., 2009[13]

ALS12	*OPTN*	Optineurin	10p13	AD (AR)	Adult-onset. Slowly progressive atypical amyotrophic lateral sclerosis[6].	Autophagy; protein aggregation; inflammation; NF-κB regulation, membrane trafficking, exocytosis, vesicle transport, reorganization of actin and microtubules, cell cycle control.	Maruyama et al., 2010[14]
ALS13	*ATXN2*	Ataxin 2	12q24.12	AD	Adult-onset, typical ALS.	RNA processing.	Elden et al., 2010[15]
ALS14	*VCP*	Valosin-containing protein / Transitional endoplasmic reticulum ATPase	9p13.3	AD / de novo	Adult-onset, typical ALS and FTD.	Autophagy; proteasome impairment; defects in stress granules; protein aggregation; mitochondrial dysfunction; endoplasmic reticulum dysfunction.	Johnson et al., 2010[16]
ALS15	*UBQLN2*	Ubiquilin-2	Xp11.21	X-linked AD	Adult or juvenile onset[6].	Proteasome impairment; autophagy; protein aggregation; oxidative stress; axonal defects.	Deng et al., 2011[17]
ALS16	*SIGMAR1*	Sigma non-opioid intracellular receptor 1	9p13.3	AD and AR	Juvenile-onset ALS associated with FTD.	Proteasome impairment; intracellular trafficking	Luty et al., 2010[18]; Al-Saif et al., 2011[19]
ALS17	*CHMP2B*	Charged multivesicular body protein 2b	3p11.2	AD	Adult-onset, typical ALS.	Autophagy; protein aggregation.	Parkinson et al., 2006[20]
ALS18	*PFN1*	Profilin-1	17p13.2k	AD	Adult-onset typical ALS.	Axonal defects.	Wu et al., 2012[21]

ALS19	*ERBB4*	Receptor tyrosine-protein kinase erbB-4	2q34	AD	Adult-onset, typical ALS.	Neuronal development.	Takahashi et al., 2013[22]
ALS20	*hnRNPA1*	Heterogeneous nuclear ribonucleoprotein A1	12q13.13	AD / de novo risk factor	Adult-onset typical ALS; myopathy; cognitive impairment.	RNA processing.	Kim et al., 2013[23]
ALS21	*MATR3*	Matrin-3	5q31.2	AD	Adult-onset. Upper and lower motor neurons are affected. Survival duration ranges from 2–12 years[24].	RNA processing.	Marangi et al., 2017[24]; Johnson et al., 2014[25]
ALS22	*TUBA4A*	Tubulin alpha-4A chain	2q35	AD	Adult-onset. Frequent typical ALS presentation with some FTD associated cases[26].	Cytoskeleton.	Perrone et al., 2017[26]; Smith et al., 2014[27]
ALS23	*ANXA11*	Annexin A11	10q22.2	AD	Adult-late onset, classical ALS, bulbar or limb onset.	Intracellular trafficking.	Smith et al., 2017[28]
ALS24	*NEK1*	Serine/threonine-protein kinase Nek1	4q33	AD	Adult-onset, although clinical descriptions are scarce, typical ALS without dementia is described[6].	Intracellular trafficking; DNA-damage response; microtubule stability.	Kenna et al., 2016[29]
ALS25	*KIF5A*	Kinesin heavy chain isoform 5A	12q13.3	AD	Adult-onset. Classical ALS.	Axonal defects; intracellular trafficking.	Nicolas et al., 2018[30]

ALS -new	*GLT8D1*	Glycosyltransferase 8 domain-containing protein 1	3p21.1	AD	Adult-onset, both limb onset and bulbar onset ALS in a limited number of clinically described cases.	Ganglioside synthesis.	Cooper-Knock et al., 2019[31]
ALS-new	*TIA1*	Cytotoxic Granule Associated RNA Binding Protein	2p13.3	AD	Adult-onset. Associated with both ALS and FTD.	Delayed stress granule disassembly; stress granule accumulation.	Mackenzie et al., 2017[32]
ALS-new	*C21orf2*	Cilia And Flagella Associated Protein 410	21q22.3	AD	Adult-onset typical ALS and FTD[6].	Microtubule assembly; DNA damage response and repair; mitochondrial function; interacts with NEK1.	van Rheenen et al., 2016[33]
ALS-new	*DNAJC7*	DnaJ Heat Shock Protein Family (Hsp40) Member C7	17q21.2	Unknown	Adult-onset[34].	Protein homeostasis; protein folding and clearance of degraded proteins; protein aggregation.	Wang et al., 2020[34]; Farhan et al., 2019[35]
ALS-new	*LGALSL*	Galectin-related protein	2p14	Unknown	Adult-onset.	Protein function is largely unknown.	Gelfman et al., 2019[36]
ALS-new	*KANK1*	KN motif and ankyrin repeat domain-containing protein 1	9p24.3	Unknown	Adult-onset.	Cytoskeleton; axonopathy.	Zhang et al., 2022[37]
ALS-new	*CAV1*	Caveolin 1	7q31.2	Unknown	Adult-onset.	Intracellular and neurotrophic signalling.	Cooper-Knock et al., 2020[38]

ALS-new	*SPTLC1*	Serine palmitoyltransferase, long chain base subunit 1	9q22.31	AD	Juvenile-onset, variable presentation including growth retardation and cognitive dysfunction.	Excess sphingolipid biosynthesis.	Johnson et al., 2021[39]; Mohassel et al., 2021[40]
ALS-new	*ACSL5*	Long-chain Fatty Acid Coenzyme A Ligase 5	10q25.2	Unknown	Adult-onset, rapid weight-loss.	Long-chain fatty acid metabolism.	Iacoangeli et al., 2020[41]; Nakamura et al., 2020[42]
ALS-putative	*ELP3*	Elongator protein 3	8p21	Unknown	Adult-onset, typical ALS without dementia.	Ribostasis; cytoskeletal integrity.	Simpson et al., 2009[43]
ALS-putative	*DCTN1*	Dynactin	2p13	AD	Juvenile-onset, slow progressive ALS.	Axonal transport.	Puls et al., 2003[44]
ALS-putative	*PARK9*	Probable Cation-Transporting ATPase 13A2	1p36.13	AR	Juvenile-onset.	Lysosome function.	Spataro et al., 2019[45]
FTD-ALS1	*C9orf72*	Guanine nucleotide exchange C9orf72	9p21.2	AD	Adult-onset, variable penetrance and clinical features.	RNA processing; nucleocytoplasmic transport defects; proteasome impairment; autophagy; inflammation; protein aggregation (DPRs).	DeJesus-Hernandez et al., 2011[46]; Renton et al., 2011[47]
FTD-ALS2	*CHCHD10*	Coiled-coil-helix-coiled-coil-helix domain-containing protein 10	22q11.23	AD	Adult-onset, complex phenotype including ALS, FTD, ataxia, mitochondrial	Mitochondrial function, synaptic dysfunction	Bannwarth et al., 2014[48]; Johnson et al., 2014[49]

					myopathy, parkinsonism, and sensorineural hearing loss.		
FTD-ALS3	*SQSTM1*	Sequestosome-1	5q35.3	AD	Adult-onset, limb onset ALS and FTD.	Proteasome impairment; autophagy; protein aggregation; axonal defects; oxidative stress.	Fecto et al., 2011[50]
FTD-ALS4	*TBK1*	Serine/threonine-protein kinase	12q14.2	AD	Adult-onset. Can present either as a pure motor syndrome or with cognitive/behavioral dysfunction either mild or severe enough for FTD-ALS diagnosis.	Autophagy; inflammation; mitochondrial dysfunction.	Cirulli et al., 2015[51]; Freischmidt et al., 2015[52]
FTD-ALS5	*CCNF*	Cyclin F	16p13.3	AD	Adult-onset.	Autophagy, axonal defects, protein aggregation.	Williams et al., 2016[53]

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