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PHARMACOTHERAPY OF AMYOTROPHIC LATERAL SCLEROSIS: AN INSIGHT

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease of motor neurons resulting in worsening of voluntary muscles and degeneration of motor neurons in the motor cortex brainstem and spinal cord. Pathogenetic mechanism of ALS includes involvement of mitochondrial dysfunction, glutamate excitotoxicity, oxidative stress and apoptosis showing that ALS is a multifactorial disease. Major symptoms include spasticity, cognitive impairment, malnutrition and muscle cramps. As ALS still remains fatal due to several complications involved, various advances have been made in modifying the disease course. Symptomatic treatment, due to complicated symptoms, and nutrition assessment and intervention, due to the involvement of malnutrition in patients has an important role in controlling the distress caused by the disease. This article reviews the current therapeutic approaches including recent advances in pharmacological treatment strategies along with nutrition and dietary supplements based on the potential to delay onset of disease, retard the progression of disease, extend the lifespan and improve the quality of life of patients.

Keywords: Amyotrophic Lateral Sclerosis, neurodegeneration, pharmacological treatment, malnutrition.

Introduction

Amyotrophic lateral sclerosis (ALS) also known as Lou Gehrig's or Charcot disease is a fatal neuromuscular disease characterized by a rapid degeneration of motor neurons and atrophy of skeletal muscles selectively affecting the upper and lower motor neurons (Yamanaka *et al.*, 2018). ALS is the third prevalent neurodegenerative disease having an incidence of 2–3/100,000 and a prevalence of 6–7/100,000 people (Costa and Carvalho, 2016; Talbott *et al.*, 2016). Both sporadic and familial ALS is associated with spinal and cortical motor neuron degeneration (Rowland and Shneider, 2001). It is more frequently diagnosed in men than in women (Zarei *et al.*, 2015). The various neurologic regions affected are the bulbar, cervical, lumbar, and thoracic regions (Mitchell and Borasio, 2007). Core clinical symptoms includes motorneuron degeneration, weakness in limbs, respiratory failure, hyperreflexia, spasticity of arms or legs which eventually paralyzes the muscles needed to breathe, slurred speech, and difficulty in swallowing (Bonafede and Mariotti, 2017). As the patients face problem in drinking and eating, they usually develop malnutrition and dehydration putting them at risk of aspiration resulting in pneumonia (Lomen *et al.*, 2003; Pratt *et al.*, 2012). The risk factors for ALS include lifestyle, smoking, dietary factors, physical stress and exposure to pesticides (Turner, 2013; Ingre *et al.*, 2015). Various pathological pathways comprising of glutamate excitotoxicity, oxidative stress, microglia activation, ion channel and mitochondria dysfunction, apoptosis and different proteinopathies are signatures of this disorder (Zufiria *et al.*, 2016). Current treatment regimens along with dietary supplements are largely focused on relieving symptoms to improve the quality of life, improving the disease condition and increasing survival time of ALS patients (Neumann *et al.*, 2006; Pradat *et al.*, 2015).

Pathophysiology

The pathophysiological mechanism of ALS is multifactorial and several mechanisms contribute to neurodegeneration.

Glutamate Excitotoxicity

Glutamate excitotoxicity has long been suspected as a mediator in disease progression in ALS which results in degeneration of neurons (Sundaram *et al.*, 2012). Several glial and neuronal cell transporter proteins in synaptic cleft regulate the extracellular concentration of glutamate. The main transporter protein is excitatory amino acid transporters (EAAT2), thus increase in glutamate in synaptic cleft due to reduced astroglial glutamate transporter disrupts glutamate regulation (Shaw and Eggett, 2000; Ferrarese *et al.*, 2001; Allaman *et al.*, 2011). Furthermore, this causes elevation of intracellular calcium ions in the motor neurons results in neurodegeneration (King *et al.*, 2016). Therefore excessive of glutamate triggers mitochondrial damage by activation of glutamate ionotropic AMPA and NMDA receptors which results in depletion in ATP synthesis, decreased cellular oxygen consumption, oxidative phosphorylation uncoupling, and increase in formation of free radicals which in turn increases oxidative stress and various destructive biochemical processes (Heath and Shaw, 2002; Vucic *et al.*, 2014). Various studies on transgenic mutant SOD1 mouse models of ALS has showed decreased level of EAAT2 which results in overstimulation of glutamate in postsynaptic receptors causing neuronal excitotoxicity (Guo *et al.*, 2003; Zarei *et al.*, 2015).

Mitochondrial dysfunctioning

Mitochondrial dysfunctioning plays important role in neuronal death in ALS (Boillee *et al.*, 2006). Disruption in mitochondrial transport leads to accumulation of abnormal mitochondria in motor neuron, aberrations in oxidative metabolism linked to changes in electron transport chain

(ETC) activity, impaired Ca2+ homeostasis as well as ATP production (Liu *et al.*, 2004; Muyderman and Chen, 2014) which results in glutamate-receptor mediated neurotoxicity (Carriedo *et al.*, 2000). Also an increase in misfolded proteins in neuronal cells (Superoxide dismutase1 (SOD1), TAR DNA-binding protein 43 (TDP-43), RNA-binding protein FUS (FUS), C9 or f7) interact with mitochondria leading to mitochondrial dysfunctioning in ALS (Smith *et al.*, 2017). Mutant SOD1 reduces the normal activity of electron transport, causing less production of ATP (Pasinelli *et al.*, 2006). Also accumulation of mutant TDP-43 aggregates lead to mitochondrial defects in ALS (Wang *et al.*, 2013). Over expression of mutant FUS in mitochondria results in increase level of reactive oxygen species (ROS) and decreases ATP production (Stoica *et al.*, 2016). Other mitochondrial proteins such as C9orf72 are also shown to augment ROS levels thus increasing oxidative stress (Onesto *et al.*, 2016).

Apoptosis:

Dysregulation of intracellular calcium and excitotoxicity plays important role in apoptotic pathways involved in the ALS pathogenesis (Ghavami *et al.*, 2014). Dysruption in the levels of bcl-2 family of oncoproteins results in activation of apoptotic pathway (Duval *et al.*, 2018). The level of dying motor neurons and apoptotic caspases-1 and -3 is increased in the spinal cord which exhibit morphological features consistent with apoptosis (Sathasivam *et al.*, 2001). In ALS mutant SOD1 interfere with apoptotic cells which are mitochondrial-dependent, such as B-cell lymphoma 2 (Bcl-2), the protein that regulates cell death (Mattson, 2000; Steele and Yi, 2006), thus, activation of pre-apoptotic cascade releases cytochrome C in the presence of Bcl-2, which directly contributes to neuromuscular degeneration and neuronal dysfunctioning (Boillee *et al.*, 2006).

Role of ROS

Overproduction of reactive species along with the imbalance caused by the body's antioxidant enzyme systems resulting in destruction of various cellular structures, lipids, proteins, and genetic materials such as DNA and RNA (Forsberg *et al.*, 2011; Islam, 2017). In ALS, SOD1 is the major antioxidant protein which leads to cytotoxicity (Simpson *et al.*, 2004; Shin *et al.*, 2013). Mutation in SOD1 results in alterations in the activity of protein, generation of free radicals which contributes in neurodegeneration in ALS (Devasagayam *et al.*, 2004). Mutated SOD1 take electrons from other cellular anti-oxidants producing superoxide and high concentration of ROS in neuronal cells (Beckman *et al.*, 2001).

Protein degradation pathways

Misfolded proteins and protein aggregates in various cellular compartments is removed by two major protein deterioration pathways; autophagy and the ubiquitin proteasome system (UPS) (Ciechanover and Kwon, 2015). This result in muscle paralysis and premature death due is due to respiratory failure in ALS patients (Kiernan *et al.*, 2011). Any alteration in the ubiquitin proteasome system results in the formation of proteinaceous inclusions in ALS. These inclusions are found in degenerating neurons and in glial cells of ALS patients (Bennett *et al.*, 2005; Boillee *et al.*, 2006; Gal *et al.*, 2007). Autophagy leads to accumulation of mutant SOD1 and TDP-43 in ALS (Kabuta *et al.*, 2006).

Management of ALS

As ALS remains fatal, several medical interventions have vastly improved the quality of life through assisting with breathing, nutrition, mobility and communication (Corcia and Meininger, 2008). Management of ALS includes pharmacological and non-pharmacological treatments. Symptomatic treatments plays important role in controlling the major consequences of the disease. Various symptoms include spasticity, drooling, sleep disturbances, cognitive imapirement and digestive disorders leads to disease progression. All these symptoms need to be identified and can be managed through medication and non-medication therapies (Corcia and Meinninger, 2008; Galvez and Khan, 2008).

Physical therapy is given to avoid physical disability, joint contractures, abnormal stiffness that improves patient activities. Proper physical exercise helps to maintain flexibility and avoids exertion against resistance which reduces muscle pain (Ashworth *et al.*, 2006). Symptoms like spasticity can be treated by giving massage which results into muscle relaxation. Also physiotherapy needs to be done on regular basis. Daily exercises including stretching and strengthening should be done to prevent pain and stiffness (Lewis and Rushanan, 2007). Various other physical therapies, including electric stimulation, balenotherapy and occupational therapy may also help the ALS patients in daily activities (Desnuelle *et al.*, 2006).

As 80% of ALS population experience speech disturbances, speech therapy is necessary to maintain and facilitate communication. As the disease progresses, it weakens the muscles of mouth and throat by causing atrophy or spasticity. The goal of speech therapy is to manage speech and swallowing difficulties (Hanson *et al.*, 2011). Other aspects that need management are impairement in muscular component of respiratory functions is also important due to impairment in muscular component (inspiratory, expiratory and bulbar muscles) of respiratory system leading to difficulty in breathing (Prell *et al.*, 2016). Clinical evaluation of pulmonary function including Forced vital capacity (FVC), Forced expiratory volume (FEV1), Maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP or SNIP test) (Tsara *et al.*, 2010) along with blood gas analysis, blood bicarbonate level, transdiaphragmatic pressure and sleep quality (by nocturnal oximetry and polysomnography) should be done on regular basis (Howard and Orrell, 2001; Radunovic *et al.*, 2007).

Nutrition is also a major problem in ALS, as weight loss due to imbalance between calorie intake and consumption results into low body mass index as ALS occurs more frequently in low BMI (Greenwood *et al.*, 2013; Yanang and Fang, 2017). Magnitude of survival due to improved nutrition is higher than the treatment by drugs (Rosenfeld and Ellis, 2008). Duration of meals and diet should be taken seriously by patients (Dupuis *et al.*, 2008). When weight loss of >10% of bodyweight gastrostomy should be proposed (Boitano *et al.*, 2001).

Pharmacotherapy of ALS

Anti-excitotoxic agents

Glutamate excitotoxicity induced motor neuron death is involved in the pathogenesis of ALS; hence decreasing glutamate excitotoxicity is a therapeutic approach for ALS

treatment. In ALS AMPA and NMDA receptors regulate glutamate induced excitotoxicity (Limpert *et al.*, 2013). Riluzole protects neuron against excitotoxicity-induced degeneration by decreasing glutamate concentration with effect on AMPA or NMDA receptors (Mcdonell *et al.*, 2012; Geevasinga *et al.*, 2016). If given at early stage of disease talampanel, a non-competitive AMPA antagonist reduces motor neuronal calcium levels in mouse model of ALS (Pascuzzi *et al.*, 2010; Paizs *et al.*, 2011). Antibiotics like ceftriaxone protect neurons against glutamate neurotoxicity and extend survival (Rothstein *et al.*, 2005; Zhoa *et al.*, 2014). Memantine is NMDA receptor blocker used in various neurodegenerative diseases including Parkinsonism and Alzheimer's disease that attenuates excitotoxicity. Administration of memantine pre-symptomatically prolongs survival in mSOD1G93A mice in ALS (Wang *et al.*, 2005; Joo *et al.*, 2007). Gacyclidine a high affinity non-competitive NMDA receptor antagonist, delayed NMDA-mediated cell death and improves locomotor function impairement in ALS (Gerber *et al.*, 2013). Valproic acid is a histone deacteylases (HDAC) inhibitor which provided neuroprotection against glutamate or kinates induced excitotoxicity in cultured neurons. It acts by upregulating Bcl-2 and decreases the number of apoptotic cells (Ragancokova *et al.*, 2010; Lv *et al.*, 2012). A combination of valproic acid and lithium delays disease onset, reduces neurological deficits and enhances survival in ALS patients (Feng *et al.*, 2008; Boll *et al.*, 2014). Sodium phenylbutyrate a HDAC inhibitor protects cultured cortical neurons against glutathione induced oxidative stress. If given either before or after symptom onset, it prolongs survival and decreases the severity of disease in mSOD1G93A mice (Ryu *et al.*, 2003; Chuang *et al.*, 2009). Vitamin D proved to reduce excitotoxicity and improves motor performance in ALS patients (Gianforcaro *et al.*, 2013; Karan *et al.*, 2013). Lithium inhibits excitotoxic motor neuron death and provides neuroprotection. It significantly delayed disease onset and duration in organotypic spinal cord cultures. This study also suggests that lithium in combination with riluzole delayed disease progression in ALS patients (Chen *et al.*, 2003; Fornai *et al.*, 2008; Caldero *et al.*, 2010).

Mitochondrial Protectants

Mitochondrial dysfunctioning leads to decline in energy production resulting in generation of reactive oxygen species (ROS) and induces apoptosis in ALS (Pattee *et al.*, 2003, Liu *et al.*, 2004). Dexpramipexole (KNS-760704) an optical enantiomer of pramipexole enhances ATP output and decreases oxidative stress. Results of various in vitro and in vivo studies on ALS mouse models showed neuroprotective effect of dexpramipexolen (Gribkoff *et al.*, 2008). TRO-19622 (Olesoxime or mitotarget) a well tolerated drug which binds to mitochondrial proteins, protects neuronal death; delays muscle denervation, astrocytosis and microglial activation in ALS (Bordet *et al.*, 2007; Sunyach *et al.*, 2012, Lenglet *et al.*, 2014). GNX-4728 protects against motor neuron death by attenuating various inflammatory actions, and preserved neuromuscular junction (NMJ) innervations in ALS patients (Martin *et al.*, 2014). Nortriptyline an antidepressant drug and a strong inhibitor of mitochondrial permeability transition (mPT), inhibits release and activation of cytochrome c and caspase-3 in ALS patients (Wang *et al.*, 2007). Immunosuppressant cyclosporine is also an mPT inhibitor which prevents mPT assembly and stabilizes membrane thus preventing apoptosis. If given at onset of disease cyclosporine enhances the survival of ALS mice (Keep *et al.*, 2001). Creatine in a dose dependent manner improves motor performance, reduces oxidative stress, prevent mitochondrial dysfunctioning, and neuronal death in G93A mice of ALS (Kilvenyi *et al.*, 1999). P7C3 an aminopropyl carbazoles (analog of P7C3A20) decreases the neuronal impairement and increases neurogenesis. Studies showed that P7C3 protects the mitochondrial membrane against calcium and showed neuroprotective effect by improving motor performance in G93A SOD1 mouse model of ALS (Pieper *et al.*, 2010; De *et al.*, 2012; Tesla *et al.*, 2012).

Antioxidants

Oxidative stress in ALS leads to motor neurons death (Orrell *et al.*, 2008). Bromocriptine, a dopamine D2 receptor agonist act as an anti-oxidant by inhibiting cell death induced by oxidative stress, improves motor functions and extends survival of ALS patients (Iwasaki *et al.*, 1997; Contestabile, 2011; Tanaka *et al.*, 2011). To study the effect in humans a phase 2a clinical trial has been conducted to evaluate neuroprotective effect of bromcriptine mesylate in ALS (Nagata *et al.*, 2016). Vitamin C and Vitamin E are naturally occurring antioxidants taken orally in ALS patients (Halliwell, 2001). Selegiline is an antioxidant, a selective inhibitor of monoamine oxidase B increases SOD activity in the basal ganglia of rats (Knoll 1989) and it improves functional disability in ALS patients (Kwieciński *et al.*, 2001). Dehydroepiandrosterone is a steroid, act as an antioxidant when investigated in patients with ALS (Eisen, 1998). Edavarone is a newly developed free radical scavenging agent, which has been investigated in ALS patients and also in stroke (Yoshida, 2006). It is a strong anti-oxidant that prevents oxidative stress, improve motor functions and slow down the loss of physical function in ALS patients (Bhandari and Kuhad, 2018). Also it effectively decreases onset of symptom, reduces body weight loss, and neuronal cell degeneration (Ito *et al.*, 2008). Ubiquinone (Coenzyme Q10, or CoQ10) is a electron carrier, a component of mitochondrial membrane which act as a free radical scavenger (Ebadi *et al.*, 2001). Because of its antioxidant effect it has been a potential treatment agent for ALS (Mancuso *et al.*, 2010). Manganese porphyrin (AEOL-10150) showed both antioxidant and free radical scavenger properties (Rabbani *et al.*, 2007). The catalytic antioxidant AEOL 10150 extends survival and improves motor neuron activity and astrogliosis in mSOD1G93A mice (Bowler *et al.*, 2002; Crow *et al.*, 2005). Rasagiline, an inhibitor of monoamine-oxidase B used in the treatment of Parkinson's disease, has shown neuroprotection by its action on stabilizing mitochondria and slows disease progression in ALS (Barohn *et al.*, 2017). Either alone or in combination with riluzole, rasagiline improves motor performance and survival in mSOD1G93A mice of ALS (Waibel *et al.*, 2004; Oldfield *et al.*, 2007). Various metals are cyctotoxic to motor neuron (Pamphlett *et al.*, 2001). DP-109 and DP-460 are lipophilic metal chelators, they chelate calcium, copper, and zinc and significantly enhances survival, improves motor performance, reduces oxidative stress induced neuron damage and reactive astrogliosis and microgliosis in ALS G93A mice (Petri *et al.*, 2007). HFE gene is involved in the regulation of iron, and there is increased HFE polymorphism in ALS patients (Restagno *et al.*, 2007). Therefore dysregulation of iron promotes oxidative stress (Schymick *et*

al., 2007; Mitchell *et al.*, 2010). M30 and HLA20 are the multifunctional iron-chelating drugs which reduce neurotoxicity and metal chelators may become a source of treatment against ALS (Kupershmidt *et al.*, 2009; Wang *et al.*, 2011). N-acetyl-l-cysteine (NAC), an antioxidant improves survival and delays onset of motor impairement in G93A mice (Andreassen *et al.*, 2000; Olivieri *et al.*, 2001). It increases the level of glutathione peroxidase and act as a free radical scavenger in ALS (Bavarsad *et al.*, 2014).

Antiapoptotic

The expression of apoptotic gene c-Abl increases 3-fold in ALS patients which in turn reduces the cell viability in ALS. Therefore inhibition of c-Abl delays motor neuron degeneration (Katsumata *et al.*, 2012). Dasatinib is c-Abl inhibitor, decreases phosphorylation of c-Abl, inactivates caspase-3 activity and inhibits cytotoxicity in ALS (Katsumata *et al.*, 2012). The hematopoietic growth factor erythropoietin (EPO) inhibits neuronal changes induced by apoptosis (Sirén *et al.*, 2001). It has been proved to prevent early neuronal injury in female animals and delay the onset of motor dysfunctioning in ALS (Grunfeld *et al.*, 2007; Naganska *et al.*, 2010). Melatonin has both anti-apoptotic and antioxidant properties (Onur *et al.*, 2004). Studies showed that intraperitoneal injection of melatonin delays onse of disease in SOD1G93A ALS mice and reduces glutamate induced excitotoxicity in NSC-34 cells (Weishaupt *et al.*, 2006; Wang *et al.*, 2009). High-dose of melatonin is well tolerated in patients with ALS (Weishaupt *et al.*, 2006). Minocycline is an antibiotic which also act as an anti-apoptotic agent (Mejia *et al.*, 2001). By inhibiting the release of cytochrome c minocycline inactivates various apoptotic pathways, reduces reactive microgliosis, as well as p38 mitogen-activated protein kinase (Tikka *et al.*, 2001; Zhu *et al.*, 2002; Wang *et al.*, 2003). Minocycline and riluzole combination decreases the side effects and can be safer if taken together in ALS patients (Pontieri *et al.*, 2005). Minocycline improves muscle strength and delayed the onset of motor neuron deterioration in G93A and SOD1G37R mice in ALS (Kriz *et al.*, 2002; Van *et al.*, 2002). Minocycline along with creatine showed neuroprotective effect by improving motor functions and extending survival in mSOD1G93A mice (Zhang *et al.*, 2003). If given at disease onset TCH346 treatment delays disease progression, increases survival, and reduces body weight and prevents neuronal apoptosis in ALS (Sagot *et al.*, 2000; Groeneveld *et al.*, 2004). zvAD-fmk is a broad caspase inhibitor that slowed disease onset and improves mortality in mSOD1G93A mice. Caspase-1 activity is inhibited by zvAD-fmk but it also inhibits caspase-1 and caspase-3 mRNA upregulation in ALS (Li *et al.*, 2000).

Anti-inflammatory

N-acetyl-Ltryptophan, an antagonist of neurokinin 1 receptor (NK-1R), inhibits cytochrome c release, decreases inflammation, regains NK-1R levels, improves motor functions and gross atrophy, and extended survival in ALS (Li *et al.*, 2015). The basic function of TNF-α is to activate microglia and introduce neuronal apoptosis in ALS (Minghetti *et al.*, 2005). TNF-α production is inhibited by thalidomide and its analog lenalidomide which results in the reduced expression of proinflammatory cytokines, significantly preserves motor performance and extends survival in ALS (Kiaei *et al.*, 2006). JGK-263 a GSK-3 inhibitor improved motor function and decreases caspase-3 activity in transgenic SOD1-G93A mice of ALS (Koh *et al.*, 2007; Ahn *et al.*, 2014). Melittin an anti-inflammatory agent reduces the level of inflammatory proteins in the lungs and spleen and the organs affected by ALS thus helps in regulating immune system (Lee *et al.*, 2014). It improves motor function and reduces the neuronal death in animal model of ALS (Yang *et al.*, 2011). 2B3-201 liposomal methylprednisolone is an anti-inflammatory agent decreases motor neuron loss in ALS and also reduces vacuolation in brainstem nuclei (Evans *et al.*, 2014). Withaferin A, a nuclear factor-kappa B (NF-κB) inhibitor, decreases neuroinflammation and reduces loss of motor neurons (Swarup *et al.*, 2011; Patel *et al.*, 2015). Cannabinoids showed anti-inflammatory properties through both its receptors i.e cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). Cannabinoids ameliorate disease progression and delays motor deterioration and enhances survival when given either before or after disease onset in ALS mice (Raman *et al.*, 2004; Shoemaker *et al.*, 2007).

Drugs restoring protein homeostasis

Arimoclomol stabilizes heat shock protein (HSF-1) delays disease progression in mSOD1G93A mice in ALS (Pandya *et al.*, 2013). It extends the life span and improves motor function and reduces ubiquitin aggregates in G93A mice of ALS (Kalmar *et al.*, 2008). Ubiquitinated proteins accumulation results in UPS failure and/or autophagy, showing arimoclomol role in protein aggregation (Kieran *et al.*, 2004). Pyrimethamine (Daraprim), used in treatment of malaria and toxoplasmosis, it reduces SOD1 levels in cultured neuronal cells in ALS (Lange, 2008). Berberine leads to increased clearance of aggregate prone TDP-43 fragments in N2a cell (Chang *et al.*, 2016)

Symptomatic treatments

Spasticity- Spasticity is common in ALS patients, however only a few percentages of patients need therapy. Muscle relaxants baclofen and tizanidine are used in the treatment of ALS. Baclofen is given via an intrathecal pump to the patients who have severe and disabling spasticity. Cannabinoids are approved in patients having multiple sclerosis and also used as a self-prescribed medicine in patients with ALS (Amtmann *et al.*, 2004).

Muscle cramps- Muscle cramps cause pain in about one-fourth of the patients having ALS which is due to the instability of motor units. Quinine sulphate, Levetiracetam and Mexiletine are the drugs commonly used for muscle cramps. In fact, Mexiletine greatly decrease the extremity of the muscle cramps in randomized control phase II clinical trials in dose dependent manner in patients with ALS (Weiss *et al.*, 2016). Quinine sulfate is used for muscle cramps, but it has some side effects like bradycardia, cardiac arrhythmias and prolongation of QT interval, therefore the FDA has advised against its use (Stephens *et al.*, 2017).

Cognitive impairement: Frontotemporal impairment is the basic reason for cognitive impairement which includes change in personality and behavior and impairments in language (Miller *et al.*, 2009). In some patients of ALS frontrotemporal dementia is also seen (Foley, 2015). Depression and anxiety has been seen to impair quality life in ALS patients (Lou *et al.*, 2003). Management of cognitive impairement combines drugs along with psychotherapy;

tricyclic antidepressants (TCAs), SSRIs or other antidepressants can be used. Amitriptyline is given to improve muscle weakness which may also help in sleep disturbances, sialorrhoea and emotional lability. For anxiety, benzodiazepines and SSRIs, buspirone and mirtazapine respond well ensuring that symptoms of respiratory impairement are significantly controlled (Kurt *et al.*, 2007; Miller *et al.*, 2000).

Urinary incontinence: Urinary urgency is very common in ALS, especially in those with leg spasticity, and impaired mobility (Mayadev *et al.*, 2008). Avoiding alcohol and caffeine is suggested to ALS patients (Nelson *et al.*, 2000). Oxybutynin is inexpensive and commonly tried in ALS patients can be crushed and given via PEG tube. Oxybutynin skin patches can be used along with oral tablets (Jackson *et al.*, 2015). Tolterodine tartrate, darifenacin, solifenacin, Trospium, and Fesoterodine (Toviaz) are also given. Also anticholinergic are given as an alternative such as amitriptyline but they may produce dry mouth, drowsiness along with confusion and dementia especially in elderly patients (Gorden *et al.*, 2013).

Nutrition and dietary supplements:

Malnutrition in ALS patients is well known and may shorten survival (Rosenfeld and Ellis, 2008). The cause of malnutrition is multiple, poor calorie intake is basically due to dysphagia which impairs the immune system and leads to infection. Due to this weight loss and below normal body mass index (BMI) is common amongst ALS patients. Thus improving nutrition is the important component in the treatment of ALS (Mattson *et al.*, 2007). Few dietary supplements are mentioned below.

- **Catechins:** Catechins are potent antioxidants and include various active constituents such as epigallocatechin, epicatechin, and epicatichin-3-gallate. They act as free radical scavengers highly present in tea, cocoa, berries, prune juice, and red wine. Catechins showed neuroprotective effects in ALS by reducing oxidative stress induced mitochondrial dysfunctioning and they cross blood-brain barrier In vitro studies showed that epicatichin-3-gallate treatment reduces glutamate excitotoxicity in SOD1 motor neurons (Xu *et al.*, 2006). Epigallocatechin-3-gallate also decreases oxidative stress, leading to motor neuron protection in the culture of a rat spinal cord (Che *et al.*, 2017).
- **Coenzyme Q10:** Coenzyme Q10 (CoQ10) a mitochondrial cofactor vitamin helps to generate energy in cells. It is found in mitochondria and thus increase ATP generation. Coenzyme Q10 protects cells from oxidative stress. Food containing CoQ10 includes fatty fish, spinach, legumes and soyabean oils (Ferrante *et al.*, 2005). Coenzyme Q10 extended survival in mouse model of ALS. Studies suggested that treatment with CoQ10 significantly attenuated neuronal damage in various neurodegenerative diseases (Flint, 2002).
- **Creatine:** Creatine is a natural component that helps in production of cellular energy in various neurodegenerative diseases (Adhihetty *et al.*, 2008). It is given in athletes to improve muscle mass. In addition, it also acts as an antioxidant, anti apoptotic and decreases glutamate excitotoxicity thus playing important role in neurodegenerative disease (Bender and Klopstock, 2016). Creatine supplements protects against loss of neurons and act as a free radical scavenger by reducing oxidative damage in ALS (Beal, 2011). In ALS, creatine supplement was found to improve motor performance, improve weight maintenance, and extend survival in G93A transgenic mice (Kaufmann *et al.*, 2009; Adhihetty *et al.*, 2008).
- **Ibedenone**: Idebenone is similar to CoQ10 that was used to treat neurodegenerative disorders. Idebenone seems to have antioxidant activity, and appears to protect a wide variety of cells from oxidative stress, also shown to inhibit lipid peroxidation in brain mitochondria (Atassi *et al.*, 2010).
- **L-carnitine**: It plays an important role in production of energy by transporting fatty acids into the cells (Binienda *et al.*, 2003). It is used as an antioxidant reduces mitochondrial injury and cell apoptosis in ALS (Jaber *et al.*, 2015; Gulcin *et al.*, 2006). Studies demonstrated that oral administration of L-carnitine significantly delayed onset of signs and delayed deterioration of motor neurons and improved life span in transgenic mice carrying a human SOD1 gene (Kira *et al.*, 2006).
- **Omega-3**: These are polyunsaturated fatty acids found in fish and nuts. It has been shown that Omega-3 reduces neuroexcitotoxicity and neuroinflammation and activates antiapoptotic pathways (Beghi *et al.*, 2013; Calder *et al.*, 2009). It has been shown that Omega-3 supplements have shown significant improvement in motor neuron pathology in murine model of familial ALS (Boumil *et al.*, 2017).
- **Resveratrol**: It is a polyphenol found in the skin of grapes, blueberries, raspberries, and mulberries. Studies has reported that resveratrol treatment delays the onset of symptoms and improves locomotor activity showing neuroprotective effects in SODG93A ALS mice (Fitzgerald *et al.*, 2014; Yip *et al.*, 2013; Mancuso *et al.*, 2014). Dietary supplementation of resveratrol improves motor neuron functioning and modulates acetylation of p53 in SOD1 mutant mice (Markert *et al.*, 2010).
- **Homocysteine**: Homocysteine is a natural occurring amino acid. It has been reported that higher plasma level of homocysteine leads to early disease progression (Crochemore *et al.*, 2009).
- Thiamine and Riboflavin supplements are also given to the patients of ALS (Hemendinger *et al.*, 2011; Song *et al.*, 2013).
- **Cannabis:** Cannabinoids found in cannabis helpful in managing clinical symptoms in ALS. In various clinical and preclinical studies cannabis has shown anti-oxidant, anti-inflammatory and neuroprotective effect in various CNS disorders (Zhoa *et al.*, 2008; Giacoppo and Mazzon, 2016). It reduces pain, improves appetite in ALS patients. It also helps in sleep and mood disturbances (Witting *et al.*, 2004; Carter *et al.*, 2001). Treatment with cannabis improves motor performance and increases survival rate in hSOD (G93A) mice by reducing glutamate excitotoxicity and oxidative stress (Raman *et al.*, 2004). Cannabis extracts are effective to treat pain related with spasticity, painful spasms and also central pain (Collin *et al.*, 2007).

Recent drugs under Clinical Trials for ALS:

S. NO	DRUGS	CATEGORY	Route of administration	Clinical trial
1.	BIIB067	Antisense drug	Intrathecal injection	Third part of phase1 trial is initiated to evaluate long term safety and tolerability (clinical trails.gov NCT02623699)
2.	Tocilizumab	Interleukin-6 receptor antagonist	Intravenous	Phase II (clinical trials.gov NCT02469896)
3.	Triumeq	Antiretroviral	Intravenous	Phase II(clinical trials.gov NCT02868580)
4.	Ibudilast	Phoshodiesterase 4 (PDE4) inhibitor	Orally	Phase III(clinical trials.gov NCT02714036)
5.	Tamoxifen	Inhibition of protein kinase C	Orally	Phase II (clinical trials.gov NCT00214110)
6.	Ezogabine	Reduce motor neuron excitability	Orally	Phase II(clinical trials.gov NCT02450552)
7.	Cistanche total glycosides (CTG)	Anti-apoptotic agent	Orally	Phase II(clinical trials.gov NCT00753571)
8.	Mastinib	Tyrosine kinase inhibitor	Orally	Phase III (clinical trials.gov NCT02588677)

Conclusion

ALS is a fatal motor neuron disease. To understand the pathophysiology as well as helping patients to improve symptoms many multidisciplinary treatment approaches can be initiated to improve the quality of life and extend the survival period. This review focuses on multidisciplinary approach includes symptomatic treatment, nutrition supplements, physical therapy and speech therapy including wide range of treatment modalities. Also management of nutrition plays an important role in ALS patients. Increasing symptoms due to malnutrition can be managed through dietary modification and supplements. Therefore, for better results proper management and patient counseling should be provided to the patients.

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