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Symptom Management and End of Life Care

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Synopsis

The number of available symptomatic treatments has markedly enhanced the care of patients with Amyotrophic Lateral Sclerosis (ALS). Once thought to be “untreatable”, patients with ALS today clearly benefit from multidisciplinary care. The impact of such care on the disease course, including rate of progression and mortality, has surpassed the treatment effects commonly sought in clinical drug trials. Unfortunately, there are few randomized controlled trials of medications or interventions addressing symptom management which has resulted in the need for physicians to base their selection of specific therapies upon personal experience and anecdotal reports (1 Forsheew). In this review, we will provide the level of evidence, when available, for each intervention that is currently considered “standard of care” by consensus opinion.

Keywords

Sialorrhea; pseudobulbar affect; non-invasive ventilation; secretion management; laryngospasm; edema; urinary urgency; constipation; depression; anxiety and end of life issues

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Sialorrhea

Sialorrhea is a socially embarrassing symptom related to pharyngeal muscle weakness which can lead to aspiration pneumonia, the most common cause of death in ALS other than respiratory failure. The prevalence of the sialorrhea among ALS patients is estimated at 50% (2 Sufit). Patients frequently have to wipe their mouth with a tissue, or in extreme cases, may need to insert a paper towel or washcloth into their mouths to absorb the saliva.

The American Academy of Neurology practice parameter for the care of ALS patients published in 1999 recommended both pharmacologic interventions and non-pharmacologic approaches such as suctioning (3 Miller). Treatment with anticholinergic medication (Table 1) (4 Jackson) is considered “first line” pharmacologic therapy, however, the benefits of this class of medication can be insufficient to completely address the symptom. In addition, common side effects associated with anticholinergic therapy include constipation, fatigue, impotence, urinary retention, blurred vision, tachycardia, orthostatic hypotension and dizziness. These side effects occur most commonly in elderly patients. In addition, anticholinergic medications are relatively contraindicated in patients with a history of glaucoma, benign prostatic hypertrophy, or cardiac conduction disorders (especially bifascicular block, left bundle-branch block and a prolonged QT interval).

Selection of a particular medication often depends upon the severity and frequency of the drooling. Sialorrhea associated with mealtimes or a particular time of day may be treated with “prn” administration of atropine, hyoscyamine or glycopyrrolate. Transdermal scopolamine, botulinum toxin or antidepressant medications provide a more continuous effect. Patients who have difficulty swallowing medications may prefer an agent that can be given sublingually, transdermally, or is available in a liquid form that can be administered directly through a PEG tube.

Data from the national ALS Patient CARE database indicate that over 70% of ALS patients treated with atropine, glycopyrrolate, or amitriptyline reported these modalities were helpful (2 (2 Sufit, 4 Bradley). By inference, approximately 30% of patients were not helped by these therapies. There remains, to date, no randomized trial comparing the efficacy of these different agents in the ALS population. In general, all of these medications may cause or aggravate existing problems with constipation, and therefore it is recommended that a stool softener be initiated at the same time the anti-cholinergic agent is prescribed.

Botulinum toxin is the newest mode of sialorrhea therapy and has, thus far, shown to have great promise in patients resistant to conventional medical therapy (6 Portis, 7 Geiss, 8 Rowe, 9 Bhatia, 10 Jackson). In a double-blind, controlled trial of botulinum toxin type B (BTxB) in 20 patients with ALS with refractory sialorrhea (10 Jackson), patients were randomized to 2,500 U of BTxB or placebo into bilateral parotid and submandibular glands. Treated patients reported a global improvement of 82% at 2 and 4 weeks compared to 38% in placebo ($p < 0.05$). At 12 weeks, 50% of patients receiving BTxB were improved compared to 14% receiving placebo. There were no significant adverse events.

Radiation therapy for medically refractory sialorrhea reduced salivary production, but side effects included erythema, sore throat, and nausea (11 Harriman). A “satisfactory response”

was observed and saliva secretion rate diminished with a single dose of 7–7.5 Gy bilaterally (12 Andersen).

Based on the AAN Practice Guidelines published in 2009 (13 Miller), in patients with ALS who have medically refractory sialorrhea, BTxB should be considered (Level B) and low-dose radiation therapy to the salivary glands may be considered (Level C).

Sticky secretions can also be problematic for a patient with ALS. These secretions may originate not only from the salivary glands but mucous from the nose and mouth may also contribute to them. (12 A Marin 1986) Sticky secretions can be a symptom of dehydration and encouraging patient to increase fluid intake may be helpful. Using a room humidifier for those not using noninvasive ventilation and bleeding humidified air into the machine for those who do may reduce their tenacity. An open label trial of 16 patients with thick secretions that had failed anticholinergic therapy were treated with either propranolol 10 mg twice a day or metoprolol 25 mg twice a day found that 75% of patients reported decreased secretions with sustained short-term efficacy in most. (12 B Newall 1996) Drinking papaya or pineapple juice, and reducing caffeine, milk or alcohol have been anecdotally suggested (Radunovic 12 C).

Pseudobulbar Affect

Pseudobulbar affect (PBA) affects 20%–50% of patients with ALS, especially in patients with bulbar onset. (14 McCullagh) The characteristics of PBA include uncontrolled laughter or crying, often with minimal or no provocation. Episodes are often sudden, involuntary outbursts of emotion inappropriate to the context of the situation. Patients experiencing uncontrolled crying are more common than those with uncontrolled laughter, however, the symptoms can result in significant disability, limiting social interactions and impairing quality of life (QoL).

Although it is not a mood disorder, selective serotonin reuptake inhibitors, tricyclic antidepressants and some serotonin-norepinephrine reuptake inhibitors have been used for treatment of PBA (Table 2) (4 Jackson).

A novel combination of dextromethorphan (20mg) and quinidine sulfate (10mg) (Nuedexta™) has been shown to be effective in a large phase three multicenter randomized trial (15 Brooks). Nuedexta patients reported significantly less emotional lability, improved QoL and improved quality of relationship scores. Side effects included dizziness, nausea, and somnolence. These side effects can be minimized by initiating the dose at 1 tablet at bedtime for 7 days followed by twice a day dosing. The AAN Practice Guidelines (13 Miller) recommend that if side effects are acceptable, dextromethorphan/quinidine should be considered for symptoms of pseudobulbar affect in patients with ALS (Level B).

Sleep disruption

Sleep disruption in patients with ALS is frequently multifactorial in etiology and may be due to respiratory muscle weakness, difficulty re-positioning in bed, anxiety, depression and pain. Nocturnal hypoventilation results in frequent arousals and decreased total sleep time

resulting in daytime fatigue and poor concentration. Overall, impaired sleep can markedly affect QoL and likely impact prognosis.

Available solutions to address impaired sleep are as varied as the diverse issues causing it. Simple physical adaptations such as an electric hospital bed can be ideal to enhance mobility and positioning. An alternating pressure air mattress or gel overlay mattress can lessen the discomfort from limited mobility. Noninvasive positive pressure ventilation can significantly affect respiratory hygiene and improve sleep quality. Antidepressant medications are also effective at reducing anxiety, depression and promoting sleep. In that regard, mirtazapine (15mg qhs) can be especially helpful. At higher doses (30 mg) mirtazapine may have a confounding effect due to enhancement of its noradrenergic effect. The anticholinergic action of the tricyclic antidepressant group can also be especially helpful, particularly in patients with sialorrhea.

Anxiolytic medications such as benzodiazepines, used specifically to induce sleep, can be helpful when used selectively. Zolpidem tartrate (10mg qhs) is often effective and preferred due to the low risk of respiratory depression. Pharmacological tolerance and withdrawal symptoms can become evident, however, with chronic use. Addressing the underlying cause of such anxiety (depression, fear, pain etc) is a preferred method of treatment.

Alternative pharmacologic agents such as melatonin, passionflower, lavender, and hops have been effective for individual patients, however, their benefits are quite variable and untested.

Respiratory Insufficiency

Patients with ALS commonly develop respiratory failure as a result of decreased diaphragmatic and intercostal muscle strength and impaired glottis function resulting in an ineffective cough. (16 Arnulf). Dyspnea is an uncommon presenting symptom of chronic respiratory failure. Rather, patients usually present insidiously with symptoms related to nocturnal oxygen desaturations such as frequent nighttime arousals, morning headache, excessive daytime sleepiness, orthopnea and fatigue.

Patients with ALS should have an assessment of pulmonary function every 3–6 months. FVC is the most commonly used respiratory measurement in ALS and is a significant predictor of survival (17 Czaplinski). In most cases, however, the earliest detectable abnormality is a reduction in maximum inspiratory pressure (MIP), sniff nasal pressure (SNP), sniff trandaphragmatic pressure (sniff Pdi) or nocturnal oximetry (desaturations <90% for 1 cumulative minute) (18 Jackson). Supine FVC, although more difficult to perform, may be a better predictor of diaphragm weakness than erect FVC (19 Lechtzin, 20 Varrato).

When FVC falls below 50% of normal or the MIP is < 60cm, non-invasive ventilation should be initiated. Discussions about respiratory interventions should always take place in concert with a pulmonologist or respiratory therapist expert in managing neuromuscular patients, and the opinions and wishes of patients and family should be the prime consideration. If the topics of a living will and durable power of attorney for health care have not yet been addressed, they should be discussed. (21 Vaszar, 22 Hull)

Non-invasive ventilation (NIV) should be considered to treat respiratory insufficiency in ALS, both to lengthen survival and to slow the rate of FVC decline (Level B) (23 Miller). In a randomized controlled study, patients using NIV experienced a median survival benefit of 205 days (24 Bourke). NIV was initiated based on orthopnea with an MIP < -60 cm or symptomatic hypercapnia. FVC declined more slowly after introducing NIV (pre -2.2% /month compared to post -1.1% /month) and the decline was slower in those who used NIV >4 hours/day.

NIV has demonstrated a positive impact on QOL in several studies (Level C). (23 Miller, 18 Jackson, 25 Bourke, 26 Butz) There were improvements noted in energy, vitality, (25 Bourke, 27 Lyall) shortness of breath, daytime somnolence, depression, concentration, sleep quality, and physical fatigue for 10 months or more. (26 Butz)

NIV may be considered at the earliest sign of nocturnal hypoventilation or respiratory insufficiency in order to improve compliance (Level C) (23 Miller, 28 Pinto, 29 Aboussouan). Orthopnea has been shown to be a strong predictor of benefit and also better compliance with NIV (24 Bourke). NIV use correlated with symptoms of orthopnea and dyspnea as well as with the use of PEG, speech devices, and riluzole (30 Jackson). Young age and preserved upper limb function have also predicted better compliance.

Noncompliance with NIV was seen in 75% of patients with ALS and frontotemporal dysfunction vs 38% in patients with classic ALS (relative risk 2.0) (31 Olney). Low compliance has also been reported in bulbar patients (24 Bourke, 32 Gruis) but cognitive/executive function was not described. Compliance can be improved by prescribing a variety of different interfaces including nasal mask, nasal pillows, full-face masks or mouth pieces in order to maximize patient comfort and minimize pressure sores. NIV should be started at low pressures to maximize a patient's tolerance to the device. Generally the inspiratory pressure (IPAP) is set at 6–8 cm H₂O and the expiratory pressure (EPAP) at 3–5 cm H₂O. The IPAP can then be titrated in 1–2 cm increments based on patient tolerance and clinical status. The device should be placed on a spontaneous timed mode with a backup rate set at the patient's nocturnal respiratory rate (generally 8–10). Frequent follow-up by a trained respiratory therapist is crucial to deal with any problems affecting patient tolerance. A heated humidifier should be prescribed if the patient develops symptoms of nasal dryness or congestion.

Expiratory respiratory muscle weakness can lead to ineffective cough, retained upper airway secretions, and pulmonary infections. PCEFs greater than 160 L/min are needed to clear secretions, (33 Bach) and when the PCEF falls below 270 L/min, (34 Tzeng) mechanical insufflation/exsufflation (MIE) may be considered to clear secretions, particularly during an acute chest infection (Level C). (23 Miller) These devices allow delivery of pressurized air (30–50 cm H₂O) followed by an immediate forced exsufflation of negative pressure (30–50 cm H₂O) for several seconds via a mouthpiece or naso-oral mask. The use of MIE safely allows patients with respiratory tract infections and profuse mucous production to clear their secretions and permit the ongoing use of NIV. MIE pressures should be set to the maximum comfortable level tolerated by each patient in order to eliminate airway secretions. In general, inspiratory pressures are set at 20–40 cm H₂O and expiratory pressures are set at 5–

20 cm H₂O. Another device useful for helping patients clear secretions is the “chest vest” that rapidly inflates and deflates resulting in a vibratory like manner up to 25 chest wall compressions/second. This helps dislodge mucous from the bronchial walls for removal via cough or a cough assist device. There is currently insufficient data to support or refute HFCWO for clearing airway secretions in patients with ALS (Level U). (Miller 23)

Medications with mucolytics like guaifenesin or N-acetylcysteine, a β -receptor antagonist (such as metoprolol or propranolol), nebulized saline, or an anticholinergic bronchodilator such as ipratropium are widely used; however, no controlled studies exist in ALS.

The Centers for Disease Control recommends that essentially all patients with significant neuromuscular illness should receive one or more doses of the pneumococcal vaccine and annual vaccines for the pertinent influenza virus. Adequate hydration must also be maintained to assure easy mobilization of secretions.

Acute respiratory failure in ALS patients is usually precipitated by an acute infection or pulmonary embolism and is seldom due to muscle weakness alone. For dyspneic or obtunded patients, emergency evaluation for endotracheal intubation may be necessary. If hypoxia alone is present and the patient is alert, oxygen at low-flow rates (< 1 L/min) may correct hypoxia although such therapy must be administered with caution, since patients with neuromuscular disease are often hypercapneic, and oxygen often depresses ventilatory drive and exacerbates hypoventilation. (35 Mangera) NIV is usually tried initially if control of secretions and cough assistance is successful. (36 Garpestad) Whether intubation or NIV is utilized, patients sometimes can be weaned following the precipitating respiratory crisis; others may require ventilation assistance indefinitely. Pulmonary consultation is always indicated in these patients.

NIV is contraindicated in patients with copious secretions, cognitive impairment, or lack of caregiver support. (37 Perrin, 38 Park) In these instances, ventilation may be more easily managed with tracheostomy and positive-pressure ventilation. (figure 1) Initiation of chronic respiratory support poses major practical, financial, medical, and ethical responsibilities for patients and families and it is often helpful for patients to discuss the procedure with others receiving such support. The input of experienced pulmonary consultants and palliative medicine services can be invaluable in these instances.

Fatigue

Fatigue is reported in 44–83% of patient with ALS and likely is multifactorial with sleep disruption, nocturnal complaints such as nocturia and cramps, nutritional status, weakness, vital capacity, functional status, depression, and medications including riluzole all potentially playing a role. (39 McElhiney 2009, 40 LoCoco 2012, 41 Ramirez 2008, 42 Bensimon 1994)) In a given patient, it may be challenging to tease out the biggest contributors, but treating those that are readily identified to see if fatigue improves is a practical approach. Overall and physical fatigue but not mental fatigue was found more often in ALS patients compared to controls. (43 Lou J-S 2003) Modafinil in doses ranging from 100 to 300 mg daily in a placebo controlled trial for 4 weeks resulted in a statistically

significant improvement in the Clinical Global Impression score (the study's primary endpoint) in 19/25 on active drug and in 1/7 on placebo ($p=0.003$) as well as improvement on the Visual Analogue Scale (VAS) for energy ($p=0.039$) and the VAS for stamina ($p=0.009$) but not in the Fatigue Severity Scale ($p=0.066$). (44 Rabkin 2009).

Nutrition

Weight loss in ALS patients may occur because of dysphagia, muscle atrophy, poor appetite related to depression, and hypermetabolic state. (45 Mascaritoli, 46 Desport, 47 Dupuis) In addition, caloric needs in an ALS patient may be underestimated using traditional equations in part because of increased work of using weak muscles, as well as energy expenditure associated with cramps, spasticity, fasciculations, and pseudobulbar manifestations. A potentially more accurate way to measure an ALS patient's total daily caloric needs uses the Harris-Benedict equation but also incorporates scores of 6 items from the ALS functional rating scale relating to speech, handwriting, dressing and hygiene, turning in bed, walking and dyspnea. (48 Kasarskis)

Weight loss of greater than 10%, (49 Limousin) rapid changes in BMI from time of symptom onset to diagnosis, (50 Shimuzu) as well as greater BMI changes in the first 2 years of being diagnosed with ALS (51 Jawaideh) are all associated with a worse prognosis. Patients with a BMI classification of mild obesity at time of study entry had a better prognosis (52 Paganoni), and in a prospective nutritional and cancer study of over a half a million subjects followed for 14–28 years, higher body fat was associated with a lower risk of dying from ALS. (Gallo 2013)

Despite this data, there is mixed evidence regarding survival benefits of providing enteral nutrition through gastrostomy tubes in patients with ALS. In the absence of randomized controlled trials, physicians are left with case controlled studies and prospective and retrospective cohort studies. (Katzberg 54). Survival benefits for those undergoing a gastrostomy include studies authored by Chiò (55) and Czaplinski (56) while examples of those finding no benefit have been reported by Forbes (57) and Mitchell (58). Possible reasons for failure to always demonstrate benefit may be patient's reluctance to do the procedure until they have lost a substantial amount of weight and so are already malnourished when the procedure is performed. Another challenge with enteral nutrition is that noncompliance with the nutritionist's recommendations is not uncommon. (61)

Enteral nutrition has resulted in stabilization and or improvement in the BMI following gastrostomy placement. (59 Desport 2000, 60 Mazzini 1995). It also allows patients to stay hydrated and provides a safe manner to administer medications. Radiographically inserted gastrostomy tubes may confer both a survival benefit (62 Chio 2004) as well as be associated with fewer insertional failures and post procedure episodes of aspiration (63 Allen 2013) compared to endoscopically placed tubes.

Only small relatively short duration studies have investigated different types of diets in patients with ALS to determine if there is a preferred diet that could influence disease progression, with variable findings as described in Table 3.

Early swallowing problems are addressed with changes made while eating, including smaller bites, slowing down, and avoiding talking while eating. Consistency changes may be suggested, including blending solid foods or adding thickener to liquids. Speech therapists may provide instructions in chin tuck or head turning to improve the ease and safety of a swallow. As the disease progresses, these are frequently not sufficient, and a feeding tube is considered. Reasons to recommend a gastrostomy tube include malnutrition/weight loss, long meal times, evidence for aspiration, and dehydration. (Miller 1999 3) Although the AAN practice guidelines supports placement when the vital capacity is above 50% because of concerns of increased risk as this value falls, (Miller 23) recent data provides evidence that a gastrostomy tube can be safely placed with vital capacities below this value, particularly when noninvasive ventilation can be used during the procedure. (Czell 68)

Pain

Pain is reported in 57 – 72% of patients with ALS and may involve the extremities, neck, back or trunk. (Pizziementi (69) Chio 2012 (70)) Pain can occur at any time during the course of the disease, and does not necessarily correlate with depression but is associated with more impaired functional status and worse quality of life. (Pizziementi (69) Ajroud (71) Pagnini (72)) While nonsteroidal anti-inflammatory drugs are frequently used, a number of therapies are prescribed including non-opioid analgesics, opioids, muscle relaxants, quinine sulfate, gabapentin, steroids, botulinum toxin, and physical therapy. (Chio 2012 (70)) The more common causes of pain are felt to be related to limited range of motion in joints, general immobility, spasticity, and or cramps. Descriptions of pain include burning, aching, cramping, and shock-like. (Newrick 73)

A Cochrane review on this subject in 2013 found no controlled or quasi-controlled studies of treating pain in patients with ALS. (74). Therefore, one cannot endorse specific ways to treat pain in ALS, though sorting out the type of pain may help the physician develop a rational approach to developing a treatment plan. In addition, if pain is related to immobility, trying to improve the comfort of what the patient sits or sleeps on, such as changing the cushion on their wheelchair or suggesting an alternating pressure mattress may be practical interventions to consider.

Spasticity

Spasticity, in addition to being a source of pain in ALS patients, can also limit mobility and function. Studies specifically investigating treatment of spasticity in ALS patients are limited. Common medications used to treat spasticity in ALS patients include baclofen, tizanidine, benzodiazepines, and dantrolene. None of these have been specifically studied in ALS, but rather in other disorders such as multiple sclerosis and cerebral palsy associated with spasticity. (Miller 23 Radunokovic 12C) One concern in using these medications in ALS patients is that they can potentially worsen weakness, which could adversely impact function. Eight patients with pain attributed to spasticity who had failed oral medication management received an intrathecal baclofen pump. There was a significant reduction in the mean pain score, and 6/8 subjects had a reduction in their pain score including 3 who became pain free. Mean pre-operative Ashworth spasticity score was 2.93 and a year

following pump placement the mean score was 1.72. (75 McClelland) In an unblinded trial, 14 patients were randomized to a moderate exercise program and 11 to their usual activities. At 3 months but not at 6 months patients performing moderate exercise showed less deterioration on the Ashworth spasticity scale; at 9 and 12 months patient dropouts made it impossible to compare the groups. (76 Drory 2001) An open label trial of levetiracetam in 20 patients found it improved cramps as well as the phasic but not tonic spasticity. (Bedlack 77) Marked spasticity of masseter muscles preventing jaw opening has been effectively treated in open label studies with botulinum toxin. (78, 79) Hydrotherapy, cryotherapy, heat, and ultrasound have also been used despite lack of controlled trials. (Anderson 2012 80)

LARYNGOSPASM

Laryngospasm is the sudden sensation that air can't be moved in and out, usually lasting seconds accompanied by inspiratory stridor, or audible respirations due to a rapid and forceful contraction of laryngeal adductors. It is extremely frightening since the patient can't take a breath or call for help. In a study on laryngospasm, 2 percent of a control group of 122 patients in the early stages of ALS reported laryngospasm (81 Sperfeld), though up to 19% of patients have reported it in later stages (1 Forsheew). Common causes of laryngospasm in ALS are liquid or saliva in contact with the larynx, acid reflux, smoke, strong smells, emotion, alcohol, cold bursts of air, and even spicy foods. Non-pharmacologic measures help in many patients. A rapid change to the upright position of the upper body, fixation of the arms to stabilize the body, breathing through the nose, swallowing repetitively and breathing with slow exhalation through lips have been reported to shorten episodes. If frequent enough and non-pharmacologic measures are ineffective, benzodiazepines bid or tid can be used. (4 Jackson, 85 Kuhnlein) In the case of GERD, treat with anti-reflux therapy and prokinetic drugs like metoclopramide before meals and at bedtime.

JAW QUIVERING/CHEEK BITING

ALS patients may report jaw quivering or clenching due to spasticity, precipitated by pain, anxiety or cold. Jaw clenching can be severe enough to interfere with oral hygiene. Treatment includes benzodiazepines as listed in Table 4. Botulinum toxin injected at 2 sites within the masseters on each side has been reported anecdotally to be effective. (4) Dental guards can alleviate cheek biting at night.

EDEMA

Dependent edema of the hands and feet occurs in weak limbs because of immobility and reduced muscle pump activity. If severe, it can be associated with painful burning sensations and fragile, easily damaged skin. Limb elevation is the primary intervention. A reclining wheelchair with leg elevation above the heart and hospital bed are probably the most comfortable and efficient, especially since the patient can reposition frequently. Moving the legs as much as possible, passive range of motion and stretching exercises performed by a caregiver several times a day, though labor intensive, are also helpful. Some patients can benefit from compression stockings, but they require proper fitting and are very difficult to put on and take off. Diuretics are avoided unless edema is severe, because fluid overload is not the issue and patients with ALS already have trouble with maintaining good hydration and diuretics worsen muscle cramps. (82 Borasio) If edema is not improved by elevating the

limbs or asymmetrical, consider evaluating the patient for deep venous thrombosis since if chronic, patients may not complain of calf pain or have erythema.

CONSTIPATION AND URINARY URGENCY

Autonomic symptoms have been reported in up to 29% of patients with ALS. (89 Piccione) Common symptoms involve urinary and gastrointestinal dysfunction. (88 Rocha) Changes in the intermediolateral columns and the Onuf nucleus provide an anatomical explanation. Causes of constipation are multifactorial and include reduced mobility, reduced fluid and food intake and medications such as anticholinergics, tricyclic antidepressants, narcotics, muscle relaxants, and sedatives. Long delays in getting to the bathroom contribute to the problem. Abdominal muscles weaken and make it difficult to expel stool, even if soft. Treatment can start with increased dietary fiber and water, as well as prune juice. Fiber laxatives (methylcellulose, bran, psyllium) are bulk forming agents and require 8 ounces of fluid (preferably water) taken immediately with each dose and maintaining good hydration to prevent intestinal blockage. In patients with dysphagia, failure to drink enough water to swallow the fiber laxative might allow swelling in the esophagus. They can also cause abdominal distension. Stool softeners are taken on a daily basis and reduce the amount of straining needed for a bowel movement. Stimulant or irritant laxatives like senna, cascara, and bisacodyl tablets and suppositories should be used at the lowest effective dose and not in slowly progressive disease as they can cause an atonic colon if used for years. They can cause abdominal cramps after each dose and if overused, fluid and electrolyte disturbances. Lactulose and polyethylene glycol are effective osmotic agents. They can cause abdominal distension, diarrhea, flatulence and nausea. More intensive treatments such as enemas, magnesium citrate and manual disimpaction are last resorts. Another option is to adjust the tube feeding formula to one with higher fiber content. Patients who are bed-ridden or receiving narcotics should be given mild laxatives prophylactically.

Urinary frequency and urgency are common in ALS patients. Some patients feel the need to urinate every 1–2 hours. For weak patients transferring to and from a toilet every few hours can be difficult and time consuming. Some patients won't leave their home because they cannot get to a bathroom fast enough and do not want to wear a diaper. Non-pharmacologic interventions include avoiding caffeine, alcohol, timed voidings, and the use of a urinal and condom catheter for men. Though physicians are reluctant to use foley catheters or refer a patient to the urologist for a suprapubic catheter, many patients are willing to accept the risk of infection and nursing care as they are no longer confined to home. Anticholinergic medications are used after urinary tract infections or an enlarged prostate is ruled out. Medications may improve urinary urgency and frequency in some patients, but not all. It is uncommon for symptoms to resolve completely. Oxybutynin is commonly tried first at 5 mg bid or tid. It is inexpensive and can be crushed and used with a PEG tube. Extended release oxybutynin at doses of 5, 10 and 15 mg are used once a day but can't be crushed for PEG tube use. Oxytrol skin patch delivers a continuous amount of medication. Tolterodine tartrate (Detrol), Darifenacin (Enablex), Solifenacin (Vesicare), Trospium (Sanctura) and Fesoterodine (Toviaz) are other options. Although beneficial, anticholinergics may produce dry mouth, constipation, blurred vision and drowsiness as well as confusion in elderly patients with dementia.

DEPRESSION AND ANXIETY

The reported prevalence of depression in ALS patients varies widely and depends on which assessment measure is used. (91 Atassi 2011, 92 Rabkin 2014) The ALS Depression Inventory (ADI-12) is a self-reported questionnaire developed specifically to screen for depression in ALS and does not refer to motor related symptoms in ALS. Using the ADI-12, Atassi et al in 2011 reported that the prevalence of mild and severe depression was 29% and 6% respectively compared to 10% of the general population with major depression. The lower rate of severe depression was attributed to patients receiving anti-depressants to treat sialorrhea, pseudobulbar affect, and insomnia, (91 Atassi 2011) The ALS Cosmos study reported that 88% of 329 patients had no depressive disorder based on structured telephone interviews. Minor depression was found in 7% and 5% had a current major depressive disorder by DSM-IV criteria. Demographic, financial and employment factors were unrelated to depression, as were duration of ALS symptoms and respiratory status. Also of the 19% of the sample who expressed a wish to die, only 37% were clinically depressed. (92 Rabkin 2014). Several classes of medications are used for the treatment of depression in ALS and are used depending on their side effect profile. There have been no controlled clinical studies of these medications in ALS patients. Tricyclic antidepressants like amitriptyline can be prescribed if anticholinergic effects are desired simultaneously for treating sialorrhea, pseudobulbar affect or insomnia.

Prevalence rates for anxiety in patients with ALS range from 0–30%. (93 Kurt 2007) The early disease phase, especially during the diagnostic period, has been reported to be associated with a higher level of stress and anxiety. (96 Vignola 2008) Anxiety is usually treated with anxiolytics like benzodiazepines, but again there have been no systematic studies of these drugs in patients with ALS. Treatment of depression and anxiety can involve both cognitive behavioral therapy and pharmacological intervention. There are no clinical trials that allow a recommendation of pharmacotherapy over psychotherapy. A positive patient-physician relationship and easy access in communicating with their physician reduces levels of anxiety in patients. Patients may benefit from a range of approaches, including relaxation strategies such as meditation and biofeedback. Cognitive behavioral therapy equips patients with the skills to overcome maladaptive thought patterns and encourages emotional readjustment.

END OF LIFE

End of life conversations can be a source of great anxiety and discomfort for the patient, their families and health care professionals, and as a result such discussions may be avoided. The issue of advance directives should be raised soon after the diagnosis. Palliative care can start any time after the diagnosis of ALS and permits the use of high tech assistive communication devices, power wheelchairs, hospitalization, non-invasive ventilation and PEG tubes. The referring physician is responsible initially for managing all medical treatment until the patient is admitted to hospice for continued palliative care. Dyspnea, despite liberal use of NIV, can be treated with morphine starting at 2.5–5 mg every 4 hours and increased in dose and frequency as needed. Anxiety and restlessness can be treated with lorazepam 0.5–2 mg every 4 hours as needed. (88 Rocha) Opiates and anxiolytics doses should be increased if they are not providing satisfactory control.

Palliative care is most often done in the hospital setting, though more community-based outpatient services have become available in large metropolitan areas. Hospice care provides interdisciplinary case management, medications, durable medical equipment and supplies. The hospice medical director manages medical treatment. Some hospices offer hospice residential care. It is appropriate for patients with FVC less than 30% of predicted, and an estimated 6 months of life. In a study of the last month of life in ALS patients, the most common symptoms were difficulty communicating, dyspnea, choking episodes, insomnia, and pain. Many of these symptoms were often inadequately controlled. (98 Ganzini) A significant number of caregivers reported depressed mood (40%), anxiety (30%) and confusion (10%) in patients. (98 Ganzini) Hospice services are essential in the management of end of life in patients with ALS and optimize the likelihood of a peaceful and dignified death. Despite its advantages, it is generally underused or initiated too late in the disease course. (99 Blackhall)

Failure to address advance directives can result in a difficult situation in which a patient who did not want tracheostomy mechanical ventilation (TMV) is intubated. Less than 10% of ALS patients in the United States use invasive ventilation (100 Rabkin 2013). Factors influencing patients against selecting invasive ventilation include high cost for home care on a ventilator, increased caregiver burden, and continued progression of the disease. Patients with TMV may end up in an extended care facility if round the clock care is not available in their home. Many caregivers report TMV at home a major burden which impacts their own health. The locked-in state occurs in 18% of ALS patients surviving more than 5 years on TMV. (101 Hayashi) Withdrawal of invasive ventilation is usually carried out with the use of high-dose opiates and benzodiazepines. A Danish palliative care study on withdrawal of invasive mechanical ventilation at home in patients with advanced ALS reported median time from discontinuation to apnea was 15 minutes (range 0–18 hours). (102 Dreyer) Doses of morphine were in the range of 60–400 mg (median 100 mg) and doses of diazepam in the range of 20–120 mg (median of 100 mg) before the ventilator was disconnected.

Summary

Patients with ALS should be provided opportunities for multidisciplinary care since the spectrum of available treatments can markedly impact both quality of life and survival. ALS should no longer be considered “untreatable” based on the broad range of interventions that can be prescribed for symptom management.

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Key Points

1. Sialorrhea should initially be treated with anticholinergic medications. For patients who remain “medically refractory”, treatment with botulinum toxin type B (Level B; recommendation by the American Academy of Neurology Practice Parameters Committee) or low-dose radiation therapy to the salivary glands (Level C) should be considered.
2. Pseudobulbar affect can be successfully treated with selective serotonin reuptake inhibitors, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors. A combination of dextromethorphan/quinidine should also be considered (Level B).
3. Non-invasive ventilation (NIV) should be considered to treat respiratory insufficiency, both to lengthen survival and to slow the rate of FVC decline (Level B). NIV has demonstrated a positive impact on quality of life (Level C). NIV may be considered at the earliest sign of nocturnal hypoventilation in order to improve compliance (Level C).
4. Mechanical insufflation/exsufflation may be considered to clear secretions, particularly during an acute chest infection (Level C).
5. Modafinil may be considered to treat fatigue if managing other contributing features fails to be effective. (Level C)
6. While enteral nutrition may help with weight stabilization, studies that have investigated possible survival benefits have provided mixed results. There is no conclusive data regarding specific diets and possible benefits in ALS. Multiple studies have found that weight loss is associated with a worse prognosis.
7. While pain is a common complaint in ALS, no controlled studies for managing it have been reported. Identifying the type and cause of the pain may be helpful in its management.
8. No controlled trials have been done investigating treatment of spasticity in ALS; medications used based upon their benefits in other disorders associated with spasticity or in open label trials in ALS include baclofen (both orally and intrathecally), tizanidine, benzodiazepines, botulinum toxin, dantrolene, and levetiracetam. Exercise intervention has also been attempted, but given the disease progression, it has been challenging to study because of high dropout rates.
9. No controlled trials have reported on the effect of treating depression and anxiety in ALS; anti-depressants are selected based upon their side effect profile. Anxiolytics and cognitive behavioral therapy are helpful in the treatment of anxiety.
10. End of life discussions are difficult for the patient, family and physician, but must not be avoided. Advance directives should be

addressed soon after the diagnosis. Hospice services are essential in the management of end of life issues in patients with ALS and optimize the likelihood of a peaceful and dignified death. Despite its advantages, it is generally underused or initiated too late in the disease course.

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Figure 1. Respiratory management algorithm

PFT = pulmonary function tests; PCEF = peak cough expiratory flow; NIV = noninvasive ventilation; SNP = sniff nasal pressure; MIP = maximal inspiratory pressure; FVC = forced vital capacity (supine or erect); Abnl.nocturnal oximetry = $pO_2 < 4\%$ from baseline.

*Symptoms suggestive of nocturnal hypoventilation: frequent arousals, morning headaches, excessive daytime sleepiness, vivid dreams, †If NIV is not tolerated or accepted in the setting of advancing respiratory compromise, consider invasive ventilation or referral to hospice.

Taken from 23 Miller

Table 1**Medications Commonly Used For Sialorrhea**

Medication	Dose
Amitriptyline	25–75 mg qhs
Nortriptyline	20–100 mg qhs
Atropine	0.4 mg q 4–6 h
	1–2 ophthalmic drops SL q 4–6 h
Glycopyrrolate	1–2 mg TID
Scopolamine patch	Apply behind ear q 3 days
Hyoscyamine sulfate	0.125 mg – 0.25 mg q 4–6 h (available as oral tabs, elixir or sub-lingual tabs)
Botulinum Toxin Type A	
Botulinum Toxin Type B	

Table 2**Medications For Treatment of Pseudobulbar Affect**

Drug	Dose	Common Side Effects
SSRI antidepressants: <ul style="list-style-type: none"> • Paroxetine • Fluoxetine • Fluvoxamine • Sertraline • Citalopram 	10–50 mg qd 10–30 mg qd 50mg qd - BID 50–100 qd - BID 20–60 mg qd	Sexual dysfunction, akathisia, sleep disturbance, anxiety
Tricyclic antidepressants: <ul style="list-style-type: none"> • Amitriptyline • Nortriptyline • Desipramine 	25–75mg qhs	Dry mouth, fatigue, dizziness, urinary retention, constipation
Mirtazapine	15mg qhs	Abnormal dreams, mild cognitive change, constipation,
Venlafaxine	37.5–75mg BID -TID	Anorexia, constipation, weight loss, impotence, anxiety, dizziness
Dextromethorphan/Quinidine	20mg/10mg 1 tab BID	Nausea, dizziness, somnolence, loose stools

Table 3

Diets studied in ALS

Author	Diet	N=	Duration	Results
Stanich 64	High protein	20	6 months	No change in muscle mass or disease progression
Silva 65	High protein	16	4 months	Stabilization of ALS-FRS-R
Dorst 66	High fat, high calorie High carbohydrate, high calorie	22 16	3 months	Wt stabilized ALS-FRS progressed High dropout rate with High carbohydrate/high calorie
Willis 67	High fat, high calorie High carbohydrate, high calorie Control	8 9 7	3 months	High carbohydrate, high calorie group had fewer adverse events, dropouts, and deaths

Table 4

Medications Used for Jaw Clenching

Medication	Dose
Clonazepam	0.5 –1 mg tid
Diazepam	2.5 –5 mg tid
Lorazepam	0.5 –1 mg tid
Alprazolam	0.25–0.5 mg tid

Table 5

Medications Used For Urinary Urgency and Frequency
(lower doses with co-morbidities)

Amitriptyline	12.5–75 mg qhs	
Oxybutynin (Ditropan) Oxytrol	2.5–5 mg bid 3.9 mg patch qd gel	Dry mouth can be significant Skin irritation, minimal dry mouth Gel without skin irritation
Tolterodine (Detrol LA)	1–2 mg bid	
Darifenacin hydrobromide (Enablex ER)	7.5–15 mg qd	Less impact on cognitive function
Solifenacin (Vesicare)	5–10 mg qd	
Tropium (Sanctura)	20 mg bid	Less interaction with CYP-450 drug
Tropium (Sanctura XR)	60 mg qd	
Fesoterodine (Toviaz)	4–8 mg qd	Superior to tolterodine
Mirabegron (Myrbetriq)	25–50 mg qd	Can't use in renal, hepatic or uncont

Table 6

Medications Used for Depression and Anxiety (Also see side effects under Table 2)

DEPRESSION	Dose
SSRI antidepressants	
Sertraline (Zoloft)	50–200 mg/d
Fluoxetine (Prozac)	10–60 mg/d
Paroxetine (Paxil)	10–50 mg/d
Paroxetine CR	12.5–62.5 mg/d
Citalopram (Celexa)	20–40 mg/d
Escitalopram (Lexapro)	10–20 mg/d
Tricyclic antidepressants	12.5–150 mg qhs
Amitriptyline (Elavil)	50–200 mg qhs
Nortriptyline (Pamelor)	50–150 mg qhs
Serotonin norepinephrine reuptake inhibitor	
Venlafaxine (Effexor)	37.5–225 mg qd
Duloxetine (Cymbalta)	
Norepinephrine dopamine reuptake inhibitor	
Bupropion hydrochloride (Wellbutrin)	300–450 mg qd
Norepinephrine serotonin modulator	
Mirtazapine (Remeron)	15–45 mg qhs
ANXIETY	
Benzodiazepines	
Alprazolam (Xanax)	0.25–1 mg tid
Lorazepam (Ativan)	0.5–2 mg tid
Diazepam (Valium)	2–10 mg tid
Clonazepam (Klonopin)	0.5–2 mg qhs
5HT1A agonists	
Buspirone	10 mg tid