

Management of endocrine conditions at the end of life

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Abstract

An important facet to end-of-life care is deprescribing. This can be challenging when reviewing life-sustaining endocrine medications but, unlike for diabetes, there is no national guidance to support patients and clinicians faced with care planning. This article reviews the limited current evidence to highlight areas for further discussion and research with the aim of moving towards consensus opinion.

Discontinuation of certain endocrine medications, including corticosteroids, desmopressin and levothyroxine, is likely to precipitate an 'endocrine-driven mechanism of death', while it may be reasonable to discontinue other endocrine medications without the risk of hastening death or causing unnecessary symptoms. However, the overarching theme should be that early discussion with patients regarding conversion or discontinuation of endocrine medications or monitoring is central to care planning.

Key words: Adrenal insufficiency; Corticosteroids; Diabetes insipidus; Endocrinology; Hypercalcaemia; Palliative

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Introduction

Almost 30% of hospital patients are in their last year of life (Clark et al, 2014) and almost 50% of people die in hospitals (Public Health England, 2018). Although endocrinopathies are not common causes of mortality, many are highly prevalent, chronic conditions that are present in patients at the end of life. Primary hypothyroidism, for example, is found in 3 in 100 of the European population (Madariaga et al, 2014). The prevalence of adrenal insufficiency following steroid use for haematological cancers is up to 60% (Broersen et al, 2015).

An important aspect of end-of-life care involves reviewing medications with an aim to discontinue any that are not providing symptomatic benefit or are potentially causing harm (National Institute for Health and Care Excellence, 2015). Deprescribing, however, is often not proactively performed. One of the four main themes that emerged about the process in a systematic review by Anderson et al (2014) was inertia, that is a tendency to avoid deprescribing despite an awareness of why it would be reasonable to do so. Accordingly, some medications might well continue to be prescribed until a person is no longer physically capable of swallowing them.

Endocrine conditions often require the use of lifelong medication and discontinuation of such medication can be life-threatening. For clinicians treating patients with diabetes mellitus, this has been considered and is reflected in the production of national guidelines (Diabetes UK et al, 2018). Diabetes UK produced their third clinical care recommendation outlining principles of treatment, with specific advice and considerations regarding common palliative conditions. Treatment aims and choice of hypoglycaemic agent for patients at the end of life are very different to those for management of diabetes in the general population (Diabetes UK et al, 2018). One major challenge is the lack of a universally-agreed definition for end of life care but Diabetes UK have helpfully provided guidance for different stages of expected prognosis.

For other endocrine conditions, there is a paucity of guidance and literature. It may not be appropriate or helpful to continue treating conditions such as growth hormone deficiency at the end of life. However, other endocrinopathies require consideration of how to adapt management to prevent avoidable deterioration in symptoms or even hasten death. Examples include the need to continue corticosteroids with sufficient mineralocorticoid

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Table 1. Endocrine medications with suggested outcomes to be discussed with patient. These decisions should be reviewed with any change in the clinical picture of the patient

Prognosis	Consider discussing discontinuation with patient	Consider optimising administration to facilitate continuation
Months to years	Growth hormone (*contraindicated with malignancy) Gonadotrophins Somatostatin analogues	
Weeks	Carbimazole	Levothyroxine – consider once-weekly dosing or subcutaneous conversion
Days to hours	Levothyroxine Fludrocortisone	Glucocorticoids – consider subcutaneous conversion Desmopressin – consider conversion to nasal spray; avoidance of fluid balance monitoring

cover when patients are no longer able to swallow, and desmopressin replacement in patients with complex fluid status.

Enhanced collaboration between oncology and endocrinology is required to meet the demands of complex medical situations (Learoyd and Clarke, 2019) and the authors advocate similar collaboration between palliative care and endocrinology to provide guidance on how to tailor care to this important population with extreme need.

This review discusses the current literature on managing patients with endocrine conditions at the end of life and provides insight into management considerations; the authors' suggestions are shown in Table 1. As there is limited evidence, the authors' aim is to highlight this important area and identify points for further discussion and study to move towards consensus opinion as opposed to providing clear guidelines on management.

General management considerations

In line with end-of-life treatment strategies for other chronic conditions, the authors advocate avoiding unnecessary monitoring and investigations while supporting discontinuation of medication that does not provide symptom relief (National Institute for Health and Care Excellence, 2015). Naturally, this must be tailored to individuals through open discussion between patients, carers and healthcare professionals about goals of care (including balancing anticipated burdens and benefits of treatment). The importance of communication should never be understated; some patients may be very resistant to stop medication that they have been repeatedly told is life-preserving. The authors suggest that these holistic discussions should involve all healthcare professionals and begin at the 'front door' of secondary care.

Observations

As a general principle, the authors propose that intensive monitoring such as strict fluid balance and other observations is not required when a person is asymptomatic and approaching the last few weeks of life. Focus upon derived investigation values is likely to generate unnecessary concern and may impede identification of other symptomatic pathologies. Individualised assessment and management of endocrine pathologies should be contextualised to anticipated longevity.

Blood sampling

Determining when to discontinue blood sampling in patients with long-term endocrine conditions can be highly challenging. As with other management decisions at the end of life, this should be individualised with full partnership from the patient. At the point when blood tests become unnecessary for other reasons, the authors propose that specific biochemical monitoring solely for endocrine conditions, for example electrolyte measurements for

diabetes insipidus, could be ceased. Organ failure will affect metabolism of medications and fluid balance estimations that would normally be reviewed in patients with diabetes insipidus.

Symptom-based adjustments to treatment may be the most pragmatic approach even before blood tests are discontinued. If the clinical status of the patient improves, then the requirement for biochemical monitoring should be reviewed; clinical context and compassion must shape clinical care and management.

Specific conditions

Active management or continuation of hormone replacement until the last few days of life is likely to be more beneficial than harmful in the following situations: cortisol deficiency, diabetes insipidus, hypercalcaemia and hypothyroidism.

Cortisol deficiency

Permanent adrenal insufficiency is present in 5 in 1000 patients in the UK; most commonly as a result of secondary causes such as hypothalamo-pituitary damage or, commonly, as a result of long-term exogenous glucocorticoid exposure suppressing endogenous cortisol production (Wass et al, 2014). Adrenal insufficiency as a result of prolonged exposure to exogenous, supra-physiological glucocorticoids (such as those used in the treatment of certain oncological diagnoses or to reduce metastasis-associated cerebral oedema) can potentially reverse and is far more common than permanent adrenal insufficiency; 50–200 per 10 000 population (Wass et al, 2014).

Non-palliative management

Whether primary or secondary, hypoadrenalism is a life-threatening condition that is conventionally managed with lifelong oral corticosteroids.

Oral hydrocortisone taken twice or three times a day with total daily doses of 15–25 mg is recommended and is the most commonly used regimen for patients with primary or secondary adrenal insufficiency (Bornstein et al, 2016). Threats to homeostasis, such as infection or sepsis, can increase cortisol production by tenfold (Nenke and Torpy, 2014), necessitating an increase in hydrocortisone dosing in patients with hypoadrenalism.

Hydrocortisone for systemic use is available parenterally as a solution and as a suspension for intramuscular or intravenous injection (Joint Formulary Committee, 2019). The only licenced parenteral formulations for use in adrenal insufficiency are intramuscular and intravenous routes.

There has been work investigating subcutaneous hydrocortisone as an alternative to either emergency intramuscular hydrocortisone or replacement to conventional long-term oral steroid regimens. The latest Endocrine Society guidance is to reserve hydrocortisone infusion therapy for those who encounter ‘major difficulty’ with conventional treatment (Bornstein et al, 2016) – this may be applicable to certain palliative patients, but this is an evolving area of practice.

Alternative replacement regimens include multiple-daily cortisone or longer-lasting, once-daily prednisolone and dexamethasone. However, dexamethasone is often not recommended for treatment of adrenal insufficiency because of the increased risk of developing a Cushingoid phenotype and its lack of mineralocorticoid action (Bornstein et al, 2016).

For patients with primary hypoadrenalism where mineralocorticoid production is impaired, including Addison’s disease, oral fludrocortisone is also required. Fludrocortisone 50–300 mcg once-daily is recommended with the dose titrated according to clinical and biochemical parameters (Joint Formulary Committee, 2019).

Literature in palliative care

In patients who can no longer take medication orally there is little literature guiding substitution for life-preserving oral gluco- and mineralocorticoids. Regional palliative care guidelines often focus upon managing weaning off supra-physiological dose glucocorticoids. Adrenal insufficiency is not listed as an indication for use of named corticosteroids, while mineralocorticoid replacement is not discussed.

- Continuation of hydrocortisone via oral, nasogastric or percutaneous endoscopic gastrostomy routes
- Once-daily prednisolone or dexamethasone (if no mineralocorticoid cover required)

Figure 1. Steroids – possible options at the end of life.

A pragmatic approach to replacement steroid dosing may be helpful. Towards the end of life, drug metabolism is likely to be different to when replacement glucocorticoids were initiated and it is important to consider this when converting between medications. Inappropriate doses may result in unwanted, distressing withdrawal symptoms or adverse effects such as psychosis at a time when the focus of treatment is directed towards minimising patient discomfort.

In the last few days of life, discontinuing supra-physiological steroids is often regarded as appropriate unless the patient is deriving significant symptomatic benefit, such as prevention of seizures or improvement in headache (West Midlands Cares, 2019).

For patients with secondary adrenal insufficiency for whom mineralocorticoid replacement is not required, with a prognosis of days to months, an equivalent dose of once-daily or continuous infusion subcutaneous dexamethasone, titrated to symptoms of withdrawal or excess, may be the most pragmatic option.

However, with reports of subcutaneous hydrocortisone as a possible suitable alternative to the conventional oral regimen (Gagliardi et al, 2014), a continuous infusion used indefinitely is a theoretically attractive option in some palliative patients with primary adrenal insufficiency. This would mirror advice advocating for continued use of insulin pumps to provide a basal rate in the last few days of life, provided that carers and the patient are comfortable with its use (Diabetes UK et al, 2018). The authors' suggestions regarding life-sustaining steroid use at the end of life are summarised in [Figure 1](#).

Diabetes insipidus

Diabetes insipidus is a rare disorder of either inadequate production of antidiuretic hormone from the posterior pituitary (central diabetes insipidus) or inadequate renal response to antidiuretic hormone (nephrogenic diabetes insipidus). Central diabetes insipidus is more common than nephrogenic diabetes insipidus and is usually secondary to trauma, surgery or tumours.

The condition leads to an inability to concentrate urine and significant polyuria. Symptoms of untreated diabetes insipidus are related to polyuria: polydipsia, fatigue, nocturia and dizziness.

If water is available and desmopressin is given appropriately, mortality is rare. However, when water intake is restricted severe dehydration, hypernatraemia and cardiovascular collapse can occur in vulnerable patients, for example elderly patients or those with intercurrent illness. Between January 2009 and October 2015, there were four patient deaths as a result of omission of desmopressin (NHS England, 2016).

Non-palliative management

The mainstay of treatment for central diabetes insipidus is desmopressin (an antidiuretic hormone analogue), adequate fluid intake and treatment of the underlying cause (Levy et al, 2019). For patients with nephrogenic diabetes insipidus, identification and treatment of the underlying cause may be coupled with high doses of intramuscular desmopressin.

In the UK, desmopressin is available as an oral tablet, sublingual melt, intranasal spray or subcutaneous, intramuscular or intravenous injection. The usual maintenance dose is oral desmopressin 0.2–1.2 mg daily, intranasally 0.01–0.04 mg and subcutaneously 1–4 mg daily (Joint Formulary Committee, 2019).

Literature in palliative care

One case report suggests that many palliative care physicians initiate a trial of desmopressin for patients with osmotic symptoms and serum sodium levels and osmolalities suggestive of diabetes insipidus, without performing a water deprivation test, stating that it would

be inappropriate in ill patients (Davis et al, 2003b). The case report also demonstrates the titration of desmopressin to symptoms of polydipsia and polyuria, rather than to fluid balance or biochemical markers (Davis et al, 2003a). Although this is an example of taking care setting into consideration, unmonitored desmopressin use in patients with possibly complex fluid balance is not without risks to health and survival.

Other than this case report, there is no further literature or guidelines specific to managing diabetes insipidus at the end of life. As described previously, the authors advocate a pragmatic, symptom-based approach to managing endocrine conditions at the end of life, diabetes insipidus included. In patients towards their last few weeks to days of life, the authors suggest focusing upon patients' perception of thirst and other symptoms of dehydration rather than strict monitoring of fluid balance or biochemical markers.

Hypercalcaemia

The most common causes of hypercalcaemia are hyperparathyroidism or malignancy (Wass et al, 2014). Hypercalcaemia of malignancy affects 10–20% of patients with advanced malignancy (Brown and Lambert, 2008) although hyperparathyroidism can obviously coexist in patients with cancer.

Symptoms of hypercalcaemia include anorexia, nausea and vomiting, bone and abdominal pain, osmotic symptoms and changes in mood and cognition (Hu et al, 2014; Walsh et al, 2016). The rate of change in calcium correlates with severity of symptoms. Hypercalcaemia can result in renal impairment, nephrogenic diabetes insipidus, pancreatitis and dysrhythmias (Brown and Lambert, 2008; Walsh et al, 2016) and is a marker of poor prognosis. In patients with hypercalcaemia as a result of malignancy, median survival is 30 days (Ralston et al, 1990).

The most common mechanism for hypercalcaemia of malignancy is secretion of parathyroid hormone-related protein that increases osteoclastic bone resorption and renal reabsorption of calcium (Brown and Lambert, 2008). Other sources of hypercalcaemia of malignancy include bone metastases causing osteoclastic bone resorption and, less commonly, paraneoplastic secretion of parathyroid hormone or active vitamin D (Stewart, 2005).

Non-palliative management

Serum calcium values ≥ 3.0 mmol/litre are likely to require treatment, particularly if >3.5 mmol/litre or the patient is symptomatic (Walsh et al, 2016).

First-line treatment is hydration with intravenous fluids and treatment of underlying causes, including discontinuation of precipitating medications such as calcium in parenteral feeds, lithium and thiazide diuretics (Stewart, 2005; Walsh et al, 2016).

If hypercalcaemia is refractory to maximal rehydration and bisphosphonate therapy, or if the patient is unable to tolerate these therapies, second-line treatments include glucocorticoids, calcimimetics or denosumab. For patients with primary hyperparathyroidism as the underlying cause, parathyroidectomy is an early intervention option.

In the authors' experience, although hypercalcaemia of malignancy is often successfully managed by parent teams with hydration and use of anti-resorptive agents, endocrinologists are consulted for further treatment options when hypercalcaemia is refractory to this treatment.

Literature in palliative care

Treatment of hypercalcaemia of malignancy is considered as a palliative strategy with an understanding that lowering the level of serum calcium will not impact upon survival (Ralston et al, 1990) and that the definitive treatment involves treatment of the underlying malignancy (Hu et al, 2014). However, effective resolution and symptom control may be achievable so the appropriateness of treatment options should be discussed with patients.

National and international palliative guidelines mirror the non-palliative guidelines for hypercalcaemia treatment, with rehydration with intravenous fluids being first line and bisphosphonates thereafter (Brown and Lambert, 2008; Scottish Palliative Care Guidelines, 2019). Another supportive measure is reduction of sedating medications to improve weight-bearing ambulation and mental clarity (Stewart, 2005).

There is no consensus regarding choice of bisphosphonate treatment, although over recent years in clinical practice, zoledronic acid has become more favoured than pamidronate.

Trial comparison is difficult because of differences in definitions of response (Brown and Lambert, 2008), so the choice should be made after considering efficacy, cost, convenience and local formulary (Scottish Palliative Care Guidelines, 2019).

Denosumab is a monoclonal antibody that binds to the RANK-ligand to prevent osteoclast formation and activity. It is used in the treatment of osteoporosis and delivered by subcutaneous injection every 4 weeks. Discontinuation of denosumab has been associated with rebound hypocalcaemia and increased vertebral fracture risk (Lewiecki, 2018).

Various case reports have demonstrated an improvement in serum calcium levels and symptoms through use of denosumab in patients with both parathyroid carcinomas (Tong et al, 2015) and other malignancies (Hu et al, 2014) causing hypercalcaemia of malignancy refractory to rehydration and bisphosphonates.

In trials, denosumab has been shown to reduce the number of adverse skeletal events, such as pathological fracture or spinal cord compression, in patients with bone metastases but had no effect upon survival, and patients treated with denosumab had higher incidences of hypocalcaemia (Henry et al, 2011). Vitamin D status and underlying renal function should be considered to minimise risk of hypocalcaemia.

Hypothyroidism

The ongoing use of thyroid hormone replacement at the end of life is likely to depend upon the prognosis of the patient; a few days or perhaps a fortnight without medication is unlikely to cause significant symptoms but not taking the medication for several months is likely to result in symptoms, if not harm.

Non-palliative management

Conventional treatment of hypothyroidism is oral levothyroxine (T4), which has a half-life of approximately a week in healthy people (ADVANZ Pharma, 2020). It is available as a tablet, capsule or oral solution and is given as a single daily dose (Joint Formulary Committee, 2019). Levothyroxine is also available as a powder for solution for injection but it is not licenced for use in the UK. There have been case reports of successful short- and long-term administration intramuscularly and intravenously in cases of variable enteral absorption, isolated levothyroxine malabsorption (Peynirci et al, 2018) and severe mental health conditions (Laycock et al, 2019).

One case report demonstrated improvement in symptoms and normalisation of biochemical markers with conversion from oral to twice-weekly subcutaneous levothyroxine in a patient compliant with high doses of combination oral levothyroxine and liothyronine (T3) (Groener et al, 2013).

Once-weekly dosing is sometimes used in patients for whom concordance is an issue and has been demonstrated to avoid thyrotoxicosis (Grebe et al, 1997; Rajput and Pathak, 2017) but may result in a trough level in the biochemically hypothyroid range before the next dose is taken (Grebe et al, 1997).

Liothyronine (T3) is an active form of levothyroxine (T4) and is not recommended for first-line use (Okosieme et al, 2016). It is available intravenously to treat myxoedema coma or orally for less severe presentation (ADVANZ Pharma, 2019). 20–25 mcg of liothyronine is equivalent to 100 mcg of levothyroxine (Joint Formulary Committee, 2019) and because of this potency it should be used with caution in patients at higher risk of cardiac disease, such as those with longstanding hypothyroidism, elderly patients and those with known cardiovascular disease (ADVANZ Pharma, 2019).

Literature in palliative care

In patients nearing the end of life, there are no publications with explicit recommendations regarding continuation of thyroid hormone replacement. Intravenous administration is of limited utility at end of life, because of the need to maintain access and continue monitoring that may be burdensome.

In the last few days of life, it would be reasonable to discontinue thyroid hormone as it is unlikely to bring any benefit. In patients expected to live for further weeks or months, continuation of once-daily oral dosing or conversion to once-weekly oral or subcutaneous dosing are options. [Figure 2](#) summarises these suggestions.

- Convert to once-weekly equivalent oral dosing
- Convert to once- or twice-weekly subcutaneous dosing
- Stop in last few days of life

Figure 2. Levothyroxine – possible options at the end of life.

Endocrine medications of limited symptomatic benefit at the end of life

Without replacement of steroids or desmopressin, patients with hypoadrenalism or diabetes insipidus respectively will die with an ‘endocrine-driven mechanism of death’ within a few days. However, other hormones are not life-sustaining and are unlikely to provide dramatic symptom relief. At a time of life where routes of administration may be more limited, the authors feel that continuation of these medications are unlikely to provide much benefit compared with the distress that may be associated with their delivery; growth hormone and gonadotrophins are examples of this.

Growth hormone is delivered by daily subcutaneous injection and, depending on national guidelines, treatment may be initiated to improve mental wellbeing and quality of life scores, improve body composition and reduce cardiovascular risk. Growth hormone replacement is generally not recommended when patients are critically unwell (Wass et al, 2014) and is contraindicated in patients with active malignancy (Joint Formulary Committee, 2019).

Gonadotrophins are delivered by subcutaneous injection to assist with fertility and are contraindicated by certain reproductive organ malignancies. The American Geriatric Society (AGS (American Geriatrics Society) 2015 Beers Criteria Update Expert Panel, 2015) recommends avoiding testosterone unless a patient has proven hypogonadism with symptoms.

Conclusions

Deprescribing is an important aspect at the end of life but when a medication is prescribed for a life-preserving indication, it can be difficult to weigh the burden and benefits clearly. A focus on adapting the administration to suit the current clinical picture is prudent to ensure effective palliative care and avoid an ‘endocrine-driven mechanism of death’.

This review has addressed the most important life-preserving medications that should be reviewed in end of life care – corticosteroids, desmopressin and levothyroxine – with a view to providing a balanced, patient-centred decision towards deprescribing. Other endocrine-related treatments can, in general, be actively deprescribed.

Death may not be a failure but poor care is. The authors hope that future collaborations and work can stem from this article to provide guidance that empowers patients, carers and their clinicians at the end of life.

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Conflicts of interest

The authors declare no conflicts of interest.

References

ADVANZ Pharma. Liothyronine sodium 20 micrograms injection. 2019. <https://www.medicines.org.uk/emc/product/2805/smpc> (accessed 17 April 2020)

Key points

- Discuss the goals of treatment with the patient and the important people in their life, where appropriate, to facilitate effective deprescribing.
- Consider conversion to non-oral options when oral medications are becoming burdensome, such as intranasal desmopressin or subcutaneous hydrocortisone infusion.
- Consider whether a patient requires mineralocorticoid cover when choosing a steroid.
- There may be merit in patients and clinicians being guided by symptoms rather than intrusive monitoring in the management of diabetes insipidus in the last few days or weeks of life.
- Hypercalcaemia is a common manifestation of advanced malignancy and management involves ensuring adequate hydration and considering second line therapies such as bisphosphonates for symptomatic benefit.
- Decisions regarding endocrine care at end of life can be complex and challenging, and involvement of senior clinicians, specialist endocrinologists and palliative care physicians can be helpful.

- ADVANZ Pharma. Levothyroxine 100 micrograms tablets. 2020. <https://www.medicines.org.uk/emc/product/5682/smpc> (accessed 17 April 2020)
- AGS (American Geriatrics Society) 2015 Beers Criteria Update Expert Panel. American geriatrics society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2015;63(11):2227–2246. <https://doi.org/10.1111/jgs.13702>
- Anderson K, Stowasser D, Freeman C et al. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. *BMJ Open* 2014;4:e006544. <https://doi.org/10.1136/bmjopen-2014-006544>
- Bornstein SR, Allolio B, Arlt W et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2016;101(2):364–389. <https://doi.org/10.1210/jc.2015-1710>
- Broersen LHA, Pereira AM, Jørgensen JOL, Dekkers OM. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2015;100(6):2171–2180. <https://doi.org/10.1210/jc.2015-1218>
- Brown E, Lambert K. Bisphosphonate infusions for hypercalcaemia of malignancy. *Eur J Palliat Care.* 2008;15(5):217–220
- Clark D, Armstrong M, Allan A et al. Imminence of death among hospital inpatients: prevalent cohort study. *Palliat Med.* 2014;28(6):474–479. <https://doi.org/10.1177/0269216314526443>
- Davis C, Kirk H, Collins S. Case study masterclass 10: presentation of lung cancer and diabetes insipidus. *Eur J Palliat Care.* 2003a;10(4):146–147
- Davis C, Kirk H, Collins S. Case study masterclass 10answers: presentation of lung cancer and diabetes insipidus. *Eur J Palliat Care.* 2003b;10(5):191
- Diabetes UK, Association of British Clinical Diabetologists, Trend UK and Diabetes Frail. End of life diabetes care: clinical care recommendations. 2018. https://www.diabetes.org.uk/resources-s3/2018-03/EoL_Guidance_2018_Final.pdf (accessed 17 April 2020)
- Gagliardi L, Nenke MA, Thynne TR et al. Continuous subcutaneous hydrocortisone infusion therapy in Addison's disease: a randomized, placebo-controlled clinical trial. *J Clin Endocrinol Metab.* 2014;99(11):4149–4157. <https://doi.org/10.1210/jc.2014-2433>
- Grebe SK, Cooke RR, Ford HC et al. Treatment of hypothyroidism with once weekly thyroxine 1. *J Clin Endocrinol Metab.* 1997;82(3):870–875. <https://doi.org/10.1210/jcem.82.3.3830>
- Groener JB, Lehnhoff D, Piel D et al. Subcutaneous application of levothyroxine as successful treatment option in a patient with malabsorption. *Am J Case Rep.* 2013;14:48–51. <https://doi.org/10.12659/AJCR.883788>
- Henry DH, Costa L, Goldwasser F et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *JCO.* 2011;29(9):1125–1132. <https://doi.org/10.1200/JCO.2010.31.3304>

- Hu MI, Glezerman IG, Leboulleux S, Insogna K et al. Denosumab for treatment of hypercalcemia of malignancy. *J Clin Endocrinol Metab.* 2014;99(9):3144–3152. <https://doi.org/10.1210/jc.2014-1001>
- Joint Formulary Committee. *British National Formulary 77: March–September 2019.* London: Pharmaceutical Press; 2019
- Laycock K, Beale C, Peters C, Anderson J. Intramuscular levothyroxine: a solution to a mental health related thyroid crisis. *BMJ Case Rep.* 2019;12(8):e228147. <https://doi.org/10.1136/bcr-2018-228147>
- Learoyd DL, Clarke SJ. Straddling medical specialties: should we have more comprehensive advanced training? *Intern Med J.* 2019;49(5):669–671. <https://doi.org/10.1111/imj.14278>
- Lewiecki EM. New and emerging concepts in the use of denosumab for the treatment of osteoporosis. *Therapeutic Advances in Musculoskeletal.* 2018;10(11):209–223. <https://doi.org/10.1177/1759720X18805759>
- Levy M, Prentice M, Wass J. Diabetes insipidus. *Br Med J.* 2019;364:1321. <https://doi.org/10.1136/bmj.2.5807.210>
- Madariaga A, Palacios S, Guillen-Grima F, Galofre J. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab.* 2014;99(3):923–931. <https://doi.org/10.1210/jc.2013-2409>
- National Institute for Health and Care Excellence. Care of dying adults in the last days of life. NICE guideline [NG31]. 2015. <https://www.nice.org.uk/guidance/ng31/chapter/Recommendations> (accessed 17 April 2020)
- Nenke M, Torpy D. Addison's disease: managing 'sick days' to avoid crises. *Endocrinol Today.* 2014;3(1):26–31
- NHS England. Patient Safety Alert - Risk of severe harm or death when desmopressin is omitted or delayed in patients with cranial diabetes insipidus. 2016. <https://www.england.nhs.uk/2016/02/psa-desmopressin/> (accessed 17 April 2020)
- Okosieme O, Gilbert J, Abraham P et al. Management of primary hypothyroidism statement by the british thyroid association executive committee. *Clin Endocrinol.* 2016;84(6):799–808. <https://doi.org/10.1111/cen.12824>
- Peynirci H, Taskiran B, Erturk E, Sisman P, Ersoy C. Is parenteral levothyroxine therapy safe in intractable hypothyroidism? *J Natl Med Assoc.* 2018;110(3):245–249. <https://doi.org/10.1016/j.jnma.2017.05.007>
- Public Health England. Statistical commentary: End of life care profiles, February 2018 update. 2018. <https://www.gov.uk/government/publications/end-of-life-care-profiles-february-2018-update/statistical-commentary-end-of-life-care-profiles-february-2018-update> (accessed 17 April 2020)
- Rajput R, Pathak V. The effect of daily versus weekly levothyroxine replacement on thyroid function test in hypothyroid patients at a tertiary care centre in Haryana. *Eur Thyroid J.* 2017;6(5):250–254. <https://doi.org/10.1159/000477348>
- Ralston SH, Gallacher SJ, Patel U, Campbell J, Boyle IT. Cancer-associated hypercalcaemia: morbidity and mortality. *Ann Intern Med.* 1990;112(7):499–504. <https://doi.org/10.7326/0003-4819-112-7-499>
- Scottish Palliative Care Guidelines. Hypercalcaemia. 2019. <https://www.palliativecareguidelines.scot.nhs.uk/guidelines/palliative-emergencies/Hypercalcaemia.aspx> (accessed 17 April 2020)
- Stewart AF. Hypercalcaemia associated with cancer. *N Engl J Med.* 2005;352(4):373–379. <https://doi.org/10.1056/NEJMcp042806>
- Tong CV, Hussein Z, Mohd Noor N, Mohamad M, Ng WF. Use of denosumab in parathyroid carcinoma with refractory hypercalcemia. *QJM-Int J Med.* 2015;108(1):49–50. <https://doi.org/10.1093/qjmed/hcu166>
- Walsh J, Gittoes N, Selby P, Society for Endocrinology Clinical Committee. Society for Endocrinology endocrine emergency guidance: Emergency management of acute hypercalcaemia in adult patients. *Endocr Connect.* 2016;5(5):G9–G11. <https://doi.org/10.1530/EC-16-0055>
- Wass J, Owen K, Turner H (eds). *Oxford handbook of endocrinology and diabetes.* 3rd edn. Oxford: Oxford University Press; 2014
- West Midlands Cares. Corticosteroids. 2019. <http://www.wmcares.org.uk/wmpcp/guide/corticosteroids/> (accessed 17 April 2020)