

# PALLIATIVE PEARLS

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## Thyroid Replacement Therapy in Hospice: Assessing Continued Benefit January 2022

Polypharmacy is the use of multiple drugs concomitantly and/or the administration of more medications than clinically indicated. Polypharmacy is especially prevalent in the elderly and can increase the risk of adverse events, decrease medication adherence, and impacts quality of life.

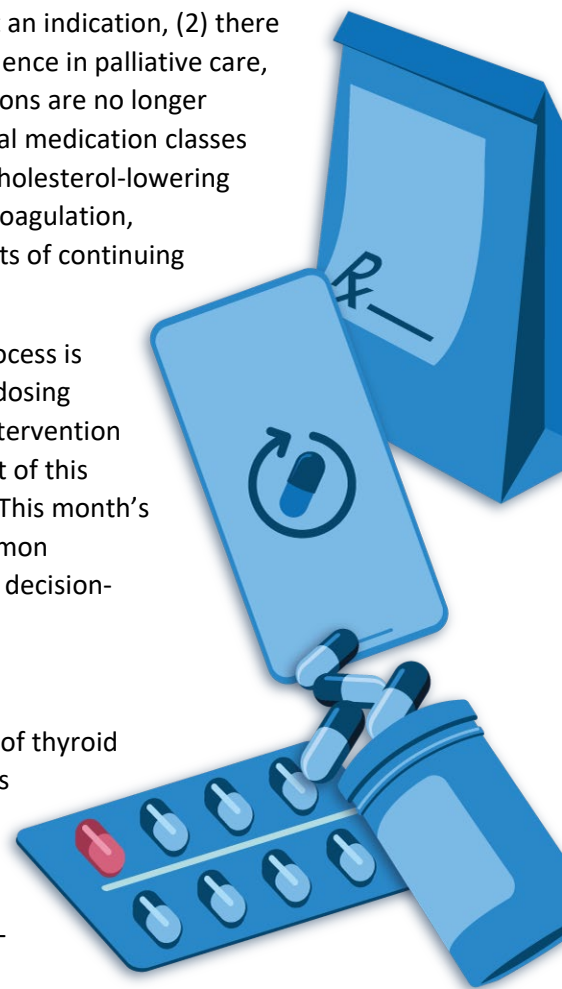
Deprescribing is “the planned and supervised process of dose reduction or stopping of medication that might be causing harm, or no longer be of benefit.”<sup>1</sup> It is a process used to mitigate polypharmacy and is especially important for patients entering hospice care when care shifts from disease prevention to symptom management.

Consider **discontinuing** medications when (1) they are prescribed without an indication, (2) there is a duplication of therapy, (3) benefit is diminished or there is lack of evidence in palliative care, (4) and when interventions used to prevent possible long-term complications are no longer aligned with care goals, and/or (5) they are causing adverse events. Several medication classes are targeted for discontinuation upon hospice admission (e.g., vitamins, cholesterol-lowering therapies) however many others require **regular re-evaluation** (e.g., anticoagulation, antihypertensives, hypoglycemics) since weighing the risks and the benefits of continuing therapy is largely patient-specific, especially when goals of care change.

One class identified for re-evaluation during the hospice deprescribing process is thyroid hormone replacement therapy (e.g., levothyroxine). Appropriate dosing and effectiveness of this therapy is driven by laboratory monitoring, an intervention many forego during hospice care. As such, assessing the continued benefit of this therapy may be challenging and solely reliant on symptom management. This month’s Palliative Pearls topic serves as a brief review of hypothyroidism and common symptoms to help reacquaint the hospice clinician and promote informed decision-making during the deprescribing process.

### TYPES

**Overt primary hypothyroidism** is a disorder resulting from the deficiency of thyroid hormone, diagnosed by elevated thyroid-stimulating hormone (TSH) levels with decreased free thyroxine (T4) or free thyroxine index (FTI). In developed countries like the U.S., where iodine intake is adequate, the most common cause of hypothyroidism is autoimmune disease. Patients are symptomatic for low thyroid.<sup>2</sup> The prevalence has been reported at 2–5% in the general population.<sup>3-6</sup>



**Subclinical hypothyroidism** is characterized by elevated TSH and normal free T4. Most patients with this type are asymptomatic; the disorder is commonly detected during routine healthcare screenings.<sup>7</sup> This type is the most common with a prevalence of 4-15% in the general population, especially in iodine-sufficient areas.<sup>5,6,8,9</sup>

**Central hypothyroidism** is caused by hypothalamic or pituitary disease and is characterized by decreased free T4 and TSH that is not relevantly elevated. TSH may be low, normal, or even slightly elevated. Patients with this type present similarly to those with overt primary hypothyroidism however with milder symptoms.<sup>7</sup> This type is rare and least prevalent.<sup>10</sup>

**History of thyroid surgery and/or radiation** due to benign or malignant conditions and resulting low TSH.

## SIGNS AND SYMPTOMS

Hypothyroidism manifests clinically in nearly all body systems including the integumentary (e.g., skin), hematologic, cardiovascular, respiratory, gastrointestinal, reproductive, neurologic, and musculoskeletal systems. Lack of thyroid hormone also manifests in metabolic abnormalities and decreases the clearance of certain medications, potentially leading to toxicity if doses are not adjusted accordingly. The major signs and symptoms of hypothyroidism occur due to either a general slowing of metabolic processes or due to the accumulation of matrix substances in the interstitial spaces of many tissues:<sup>11</sup>

- **Symptoms** include fatigue and weakness, cold intolerance, dyspnea on exertion, weight gain, cognitive dysfunction (slowed mentation, poor concentration, and poor short-term memory<sup>12</sup>), intellectual disability (infantile onset), constipation, growth failure, dry skin, hoarseness, and edema, decreased hearing, myalgia, and paresthesia
- **Signs** include slow movement and slow speech, delayed relaxation of tendon reflexes, bradycardia, carotenemia, coarse skin, puffy facies and loss of eyebrows, periorbital edema, enlargement of the tongue, diastolic hypertension, and pleural and pericardial effusions

## THYROID REPLACEMENT THERAPIES

**Levothyroxine (Synthroid®, Levoxyl®, Levotheroid®, Unithroid®, Tirosint®, Thyquidity®)**<sup>2,13</sup>

Levothyroxine (LT4) is the treatment of choice for patients with hypothyroidism.<sup>2</sup> The average full replacement dose of T4 in adults is approximately 1.6 mcg/kg/day (e.g., 112 mcg/day in a 70-kg adult), but the range of required doses is wide, varying from 50 to  $\geq 200$  mcg/day.<sup>7</sup>

Available dosage forms: Oral tablet, capsule (liquid-filled), and liquid; Solution for injection

**Liothyronine (Cytomel®, Triostat®)**<sup>2,13</sup>

Liothyronine (LT3) is a synthetic form of the natural thyroid hormone (T3) converted from T4. It is not intended for use alone, but in rare cases it can be used together with LT4 in small doses (5-15 mcg/day).<sup>2</sup>

Available dosage forms: Oral tablet; Solution for injection

## Thyroid desiccated (Armour Thyroid®, Nature-Throid®, Westhroid®) <sup>2,13</sup>

Desiccated thyroid is derived from extracts of bovine or porcine thyroid glands. Desiccated thyroid is referred to as natural thyroid and generally contains T3 and T4 in a 1:4 ratio.<sup>2</sup>

Available dosage forms: Oral tablet

### APPROACH TO DEPRESCRIBING

Unmanaged hypothyroidism affects several body systems and metabolic processes with symptoms severe enough to warrant palliation with thyroid hormone replacement therapy. Many of these symptoms are similar to those manifested by other conditions common to patients at end of life and may not be recognized as thyroid-related and overlooked by clinicians.<sup>14</sup> Examples include:

- Cognitive dysfunction in dementia
- Fatigue and poor concentration in major depression
- Dyspnea on exertion in respiratory disease
- Edema in cardiovascular disease
- Constipation unexplained by other factors

Thyroid replacement hormones have drug-drug and drug-food interactions that should be factored in when making therapy decisions:

- Certain foods, beverages, and enteral feedings can inhibit the absorption of thyroid hormones. To minimize the risk of an interaction, thyroid hormones are administered on an empty stomach with a glass of water at least 30 to 60 minutes prior to food or enteral feedings. In a population that may progress to sporadic eating, this may be difficult to manage.<sup>13</sup>
- The metabolism of several medications is affected by thyroid hormone level. When thyroid hormone therapy is initiated, it is adjusted to meet euthyroid levels. With a consistent medication regimen, most drug interactions are managed by spacing out the administration of thyroid replacement from other medications while others may be managed by adjusting the dose of the interacting medication to meet therapy goals.<sup>13</sup> However, realize on hospice care, the dose, type, and number of medications administered is not always consistent and may change with new and worsening end-of-life symptoms.

**Consider continuing treatment** of hypothyroidism among hospice patients:<sup>14</sup>

- On high doses of LT4
- With overt primary hypothyroidism with clear indications for treatment (e.g., history of Hashimoto's thyroiditis, radiation-induced or surgically induced hypothyroidism)
- Projected to have a longer survival on hospice enrollment (i.e., months)

Recent literature supports **considering a trial of tapering doses** of, and potentially discontinuing, thyroid hormone replacement therapy in patients on low doses of LT4, those with subclinical hypothyroidism and those that have been on therapy for a short duration.

- Jung KY, et al (2020) published a retrospective study including 382 patients aimed to investigate the factors predicting the successful discontinuation of LT4 therapy in patients with primary hypothyroidism. Shorter duration of LT4 therapy (less than 4.6 years) and the lower LT4 dose at the time of tapering were determined to be predictable factors for successful LT4 tapering in stable patients with overt primary hypothyroidism.<sup>3</sup>
- Burgos N, et al (2021) performed a systematic review and meta-analysis aimed at reviewing the evidence on clinical outcomes of patients undergoing thyroid hormone replacement discontinuation, identifying the predictors of successful discontinuation, and systematically appraising frameworks used for deprescribing thyroid hormone.<sup>15</sup> Seventeen observational studies were reviewed, including a total of 1103 patients (86% women) with an age range of 2-81 years. Low quality evidence suggested that approximately a third of patients undergoing thyroid hormone discontinuation remained euthyroid after LT4 discontinuation, with a higher proportion of patients with an initial diagnosis of subclinical hypothyroidism remaining euthyroid than patients with an initial diagnosis of overt primary hypothyroidism. Investigators noted that no study followed a framework for systematically deprescribing LT4.<sup>15,16</sup>

Addressing polypharmacy through deprescribing remains an integral process in the care of terminally ill patients. However, clinicians need to be judicious and consider patient-specific factors in several conditions, including hypothyroidism, before intervening. Appropriate patients may continue to benefit from thyroid hormone replacement therapy while others may be safely tapered.<sup>14</sup>

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