

# Self Medication Practices among Patients taking Levothyroxine

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## Citation

R Michel, P Neafsey, L Cox Dzurec. *Self Medication Practices among Patients taking Levothyroxine*. The Internet Journal of Advanced Nursing Practice. 2003 Volume 6 Number 2.

## Abstract

Hypothyroidism affects over 13 million people in the U.S., especially women. This condition is treated with levothyroxine sodium (Levoxyl, Synthroid, or Unithroid), which is the 2<sup>nd</sup> most commonly prescribed medication in the U.S. Patients treated with levothyroxine are at increased risk for osteoporosis and often take a calcium supplement, such as calcium carbonate. Calcium supplements are the most common type of mineral supplements sold in the U.S. Studies have shown that taking calcium carbonate within four hours of levothyroxine may decrease absorption of levothyroxine.

The objective was to determine how common it is for patients to take levothyroxine with nutritional supplements, especially calcium. Forty-five patients taking levothyroxine (mean age 51, n = 38 women) responded to posters at local pharmacies and completed a telephone survey. Over 80% of people taking calcium (n=21) reported taking it within four hours of levothyroxine. Seventy-eight percent of people taking a multi-vitamin (n=23) also reported taking it within four hours of levothyroxine.

## INTRODUCTION

Synthroid, a common thyroid hormone preparation, is the second most commonly prescribed brand medication in the U.S. (1). Calcium is the top mineral supplement sold in the U.S. by dollar sales, while multi-vitamins are the top supplement sold overall by dollar sales (2). It is likely that there is widespread use of both medications, especially in post-menopausal women. Patients who do not separate these two medications by at least four hours, or who take calcium sporadically, may not consistently achieve therapeutic levels of levothyroxine. The purpose of this study was to determine how common it is for patients on levothyroxine to self-medicate with calcium supplements and/or with multi-vitamins, and how many patients taking both levothyroxine and calcium or multi-vitamin supplements separate administration by at least four hours.

## BACKGROUND

Hypothyroidism is a condition that can cause symptoms such as dry skin, cold intolerance, muscle cramps, constipation, weight gain, and menstrual disturbances (3). Depression and fatigue are particularly troubling symptoms, and have been linked with both overt and subclinical hypothyroidism (4). This condition affects approximately 13

million people in the U.S., and is particularly common in women (3,5). The thyroid gland is underactive in hypothyroidism and does not produce enough thyroid hormone. Serum TSH (thyroid stimulating hormone) levels are high and thyroxine levels are low in the body.

Treatment for hypothyroidism most commonly involves thyroid hormone replacement in the form of levothyroxine sodium (free T<sub>4</sub>) (6). This medication is more commonly known by its several brand names, Synthroid®, Levoxyl®, and Unithroid®. Thyroid hormone replacement suppresses the elevated TSH levels and supplies the needed thyroxine. Serum levels of the hormone reach steady state after six weeks of therapy, and most patients continue to take the medication once a day for the rest of their lives (3).

Hyperthyroidism, on the other hand, is a condition in which the body produces too much thyroid hormone. TSH levels are suppressed while thyroxine levels are elevated. Excess thyroid hormone puts patients at risk for osteoporosis (7). Osteoclastic bone resorption and decreased intestinal calcium absorption can lead to bone loss (7,8,9). Treatment for hypothyroidism with levothyroxine sodium may cause exogenous subclinical hyperthyroidism, resulting in over suppression of TSH with normal thyroxine levels (9).

Consequently, many patients who take levothyroxine sodium for hypothyroidism are encouraged to take an over-the-counter (OTC) calcium supplement, such as calcium carbonate. This practice has been shown to prohibit osteoporosis induced by levothyroxine therapy (<sub>10</sub>). Calcium supplementation is especially important for post-menopausal women who are already at an increased risk for osteoporosis. This group is also the largest group of patients taking levothyroxine (<sub>10</sub>).

In 2000, Singh, Singh, and Hershman published a study indicating that calcium carbonate decreases absorption of levothyroxine, resulting in significantly decreased levels of the hormone in the body. Twenty hypothyroid patients who were taking levothyroxine in their study simultaneously ingested 1200 mg/d of elemental calcium as calcium carbonate for a period of three months. Results showed that during calcium administration, both mean T<sub>4</sub> and free T<sub>4</sub> levels were significantly reduced. However, both mean T<sub>4</sub> and free T<sub>4</sub> levels rose after calcium was discontinued. Serum thyrotropin levels also rose significantly with calcium ingestion, but dropped when calcium was stopped.

The study also included an in vitro analysis that showed that at acidic pH levels, T<sub>4</sub> adsorbs to calcium carbonate. For this reason, Singh, Singh, and Hershman suggested that patients taking calcium carbonate and levothyroxine separate the times of ingestion (<sub>10</sub>). Schneyer recommended a space of four hours between administration of these two medications to avoid the interaction (<sub>11</sub>). Both Schneyer and Butner, Fulco and Feldman reported cases in which malabsorption of levothyroxine seemed to be induced by calcium carbonate ingestion. (<sub>11,12</sub>).

More recently, Singh, Weisler, and Hershman published a study that explored the acute effect of calcium carbonate ingestion with levothyroxine. Seven participants with no evidence of thyroid disease participated in two visits in which they were given either 1000 µ levothyroxine plus 2.0 g calcium carbonate or 1000 µ levothyroxine plus placebo.

Total T<sub>4</sub> and free T<sub>4</sub> levels were measured at 30, 60, 90, 120, 240, 360, and 1,440 minutes, and TSH was measured at baseline and after 1,440 minutes. The two sessions were separated by four weeks. Results showed that calcium carbonate acutely reduced the average absorption of levothyroxine from 83.7% to 57.9%, and lengthened the time to peak absorption from 120 minutes to 240 minutes (<sub>13</sub>).

A third case report describes a woman with preexisting malabsorption disorders whose TSH increased to overtly hypothyroid levels with simultaneous ingestion of high doses of calcium carbonate with levothyroxine. Separation of the two medications by four hours and an increase of daily levothyroxine corrected the levels (<sub>14</sub>).

Ferrous sulfate has also been shown to reduce the efficacy of levothyroxine when the two are ingested simultaneously. In some patients, they may interact to produce hypothyroid symptoms. Some have suggested that a binding of iron to thyroxine causes this interaction (<sub>15</sub>). Iron is included in many OTC multi-vitamin supplements, and patients may be unaware they are at risk for this interaction when they take multi-vitamins. No research has been published about possible interactions between magnesium or zinc and levothyroxine. These supplements are still of possible concern for potential interactions. Like calcium, they are divalent minerals, which may suggest a propensity for similar malabsorption reactions with levothyroxine.

## METHODS

### DESIGN AND SAMPLE

A survey design was used. Forty-five participants taking levothyroxine were recruited. All contacted participants agreed to participate. The sample consisted of 7 men and 38 women. The mean age of participants was 51 years +/- 13.5, with a range from 20 to 78 years. Ninety-six percent (n= 43) of participants reported a high school education or better, while 47% (n=21) reported four years of college or better. All participants were taking some form of levothyroxine sodium.

### INSTRUMENT

Questions for the instrument were developed with the input of two doctorally prepared experts. A pharmacologist with expertise in drug-nutrient interactions, and a nurse practitioner with expertise in identifying individuals with thyroid disorders reviewed the instrument and provided content validity for the interview schedule.

### PROCEDURE

The university committee for human participants approved the study. To recruit participants the investigator displayed posters on pharmacy counters at four pharmacies in three small towns in New England. The posters announced a telephone survey for patients taking any form of levothyroxine. Posters were designed with input from two student focus groups at the University of Connecticut for

elements such as color, lettering, size, and wording. A Visual Communications Designer also reviewed posters for design and impact.

Attached to each poster was a stack of cards for participants who were interested in taking part in the study. The cards described an offer of a coupon for free ice cream as an inducement for participation. Participants called the number printed on the card and listened to a message asking them to leave their only first name, phone number, and a convenient time to reach them. Participants were then contacted by telephone. Although the posters were displayed at four local pharmacies in Northeastern Connecticut from June through November, 2001, most of the responses were between June and late August 2001.

Participants were told that the survey was about ten minutes long, and that they would answer questions about their health and medications. A number code was assigned to each participant so that names were not associated with answers to questions. Participants knew that they could stop at any time if they were uncomfortable and that they would still be entitled to the free ice cream coupon. All participants were given a chance to ask questions, and knew that agreeing to continue was considered informed consent.

Participants answered questions about their general health and about how, when, and why they take levothyroxine and OTC vitamins or mineral supplements, such as calcium. Participants were asked specifically if they used any OTC products for indigestion/upset stomach/gas or constipation, and if they used calcium, iron, zinc, multi-vitamins, or magnesium. After completing the survey, participants were informed about the interaction between calcium carbonate and levothyroxine. Participants were given this information regardless of whether or not they seemed to be at risk for the interaction.

## RESULTS

Seventy-six percent of participants reported that they were also currently diagnosed with various other diseases, and had been so for at least two months. Participants reported forty-six different diseases. The most commonly reported conditions were hypertension, 33%, depression, 27%, hyperlipidemia, 27%, and arthritis, 24%. Osteoporosis was reported by 13% of participants.

The mean length of time for levothyroxine use was 9.97 +/- 11.26 years. Seventy-three percent (n=33) of participants reported that they purchase OTC medications at a pharmacy

with a pharmacist.

Forty-seven percent (n=21) of the participants reported taking a calcium supplement on a regular basis. This supplement included antacids such as Tums® that were taken for reasons other than calcium supplementation. Seventy-one percent (n=15) reported using calcium to prevent osteoporosis. Of those taking calcium, 86% (n=18) reported taking the supplement within four hours of levothyroxine. Specifically, 17% took the drugs at the same time, while 50% took them within an hour of each other. Another 17% took the medications between one and two hours apart, and 11% separated calcium and levothyroxine by three to four hours. Seventy-one percent (n=15) of participants taking calcium reported that the practice was recommended to them by a healthcare professional.

Only two of the participants taking calcium reported that they knew specifically not to take it with levothyroxine. Both of these participants had been informed by patient information on pharmacy printouts. Neither had been told by a healthcare professional. When asked who prescribes their levothyroxine, 62% of all participants cited a family physician, while 27% cited an endocrinologist. If patients were interested in the safety of OTC products combined with their medications, 40% reported they would be likely to ask their pharmacist, and 33% ask their physician. Seventy-eight percent reported no problems getting information about the safety of OTC medications.

Only two participants reported taking an iron supplement, and one of them reported taking it at the same time as levothyroxine for convenience. One participant was advised to take iron by a physician, and one by a naturalist. Two participants reported taking zinc, and both had made this decision on their own. Both took zinc at least four hours before or after levothyroxine. Three people reported that they used magnesium. Two of them did so because a physician recommended it, and one decided independently. All three reported taking the magnesium within an hour of levothyroxine.

Fifty-one percent (n=23) of the all participants reported taking a multi-vitamin. Of those, 78% (n=18) reported taking it within four hours of levothyroxine. The number of participants using both calcium and a multi-vitamin supplement was 37.5% (n=17). Forty-three percent (n=10) of patients taking a multi-vitamin reported that they decided to take it on their own.

### DISCUSSION

While this study is not generalizable because of the small sample size and lack of control, the results suggest a need for teaching both patients and practitioners about the interaction between calcium carbonate and levothyroxine. Along with education of healthcare professionals who prescribe or recommend either medication, warning labels on pharmacy vials of levothyroxine may also increase patient awareness.

As these researchers reviewed patient information given by the participating pharmacies, it was found that the patient information from two of the four pharmacies did recommend separating the two drugs by at least four hours. However, it is likely that many patients do not read this information, especially if they have taken levothyroxine for many years.

Participants were asked generally about calcium and multi-vitamin supplements. Results do not show how much of the calcium being used was calcium carbonate or how many of the multi-vitamins contained iron. This information would be helpful to measure in future studies. Additionally, participants were not asked about their racial or ethnic backgrounds. In future work, these researchers would collect data about these variables to determine whether there is an interaction between race/ethnicity and self-medication practices.

Patients who have consistently taken levothyroxine with calcium carbonate for years may have had their doses adjusted so they consistently remained at therapeutic levels over time. However, patients who take calcium carbonate sporadically or inconsistently may unknowingly change the absorption of levothyroxine, causing variations in their medication levels. Further, since in typical clinical practice, the medications are adjusted annually, there could be long periods when clients would experience alterations in their medication levels and this would not be apparent to their practitioners. Clients experiencing symptoms of hypothyroidism such as fatigue or depression during a period when their blood levels of levothyroxine were low might readily be prescribed antidepressants. Antidepressants might not address the problems of low blood levels of levothyroxine.

Future studies could investigate further the appropriate time frame for separation of calcium carbonate and levothyroxine, as suggested by Schneyer.<sup>8</sup> This issue is important for patients who must manage complex medication regimens and interactions among prescribed medications. Results of this study supported that the majority of participants asked

their pharmacists and physicians about the safety of OTC products. Information on the knowledge levels of these two groups might aid further in identification of the problem. A study that examined blood levels of circulating T<sub>4</sub> among individuals taking multiple medications would help to establish the effects of taking multiple medications on T<sub>4</sub> levels as well as on hypothyroid symptoms.

Studies are also needed to investigate the possibility of interactions between other vitamins and minerals and levothyroxine, including magnesium and zinc. Due to the need for further study of calcium as well as other minerals, it seems prudent to recommend that patients on levothyroxine therapy who take any mineral supplements separate them by at least four hours to prevent any possible interactions.

Among participants in this study, it was not uncommon to take levothyroxine with other OTC medications, nor was it uncommon to combine them over a period of less than four hours. Since levothyroxine preparations are commonly prescribed, it is important to investigate the implications of this self-medication practice more fully.

This study brings two important points together. Levothyroxine is prescribed very commonly, and calcium and multi-vitamin supplements are used very frequently in the U.S. (1,2). Results suggest that patients using both these types of preparations are unlikely to separate them by sufficient time to prevent interaction. Therefore, it is likely that this interaction is widespread among patients with hypothyroidism. Certainly education of both patients and healthcare providers may decrease the risk of this interaction.

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