Associazione Medici Endocrinologi
Per la qualità clinica in Endocrinologia

# TIROIDE, DALLA GESTAZIONE ALLA TERZA ETÀ

Evento accreditato ECM

BRESCIA, 18 APRILE 2015

## La terapia sostitutiva nel paziente fragile e/o poco compliante

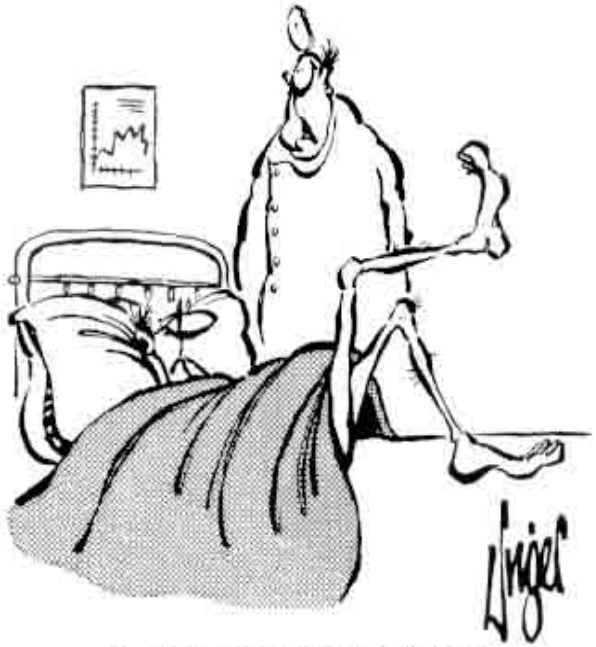
C. Cappelli, MD

Spedali Civili di Brescia

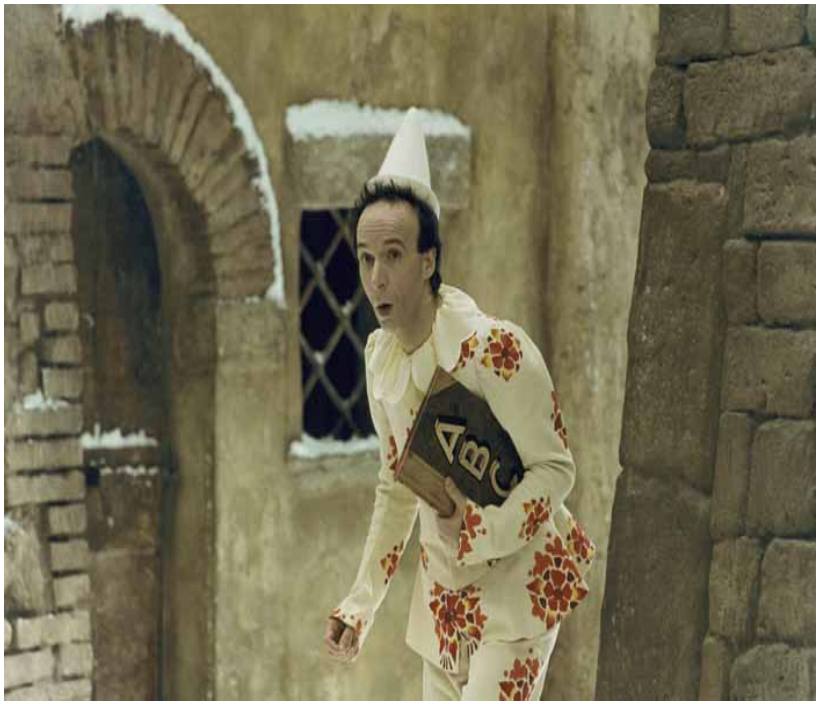
## Paziente Fragile

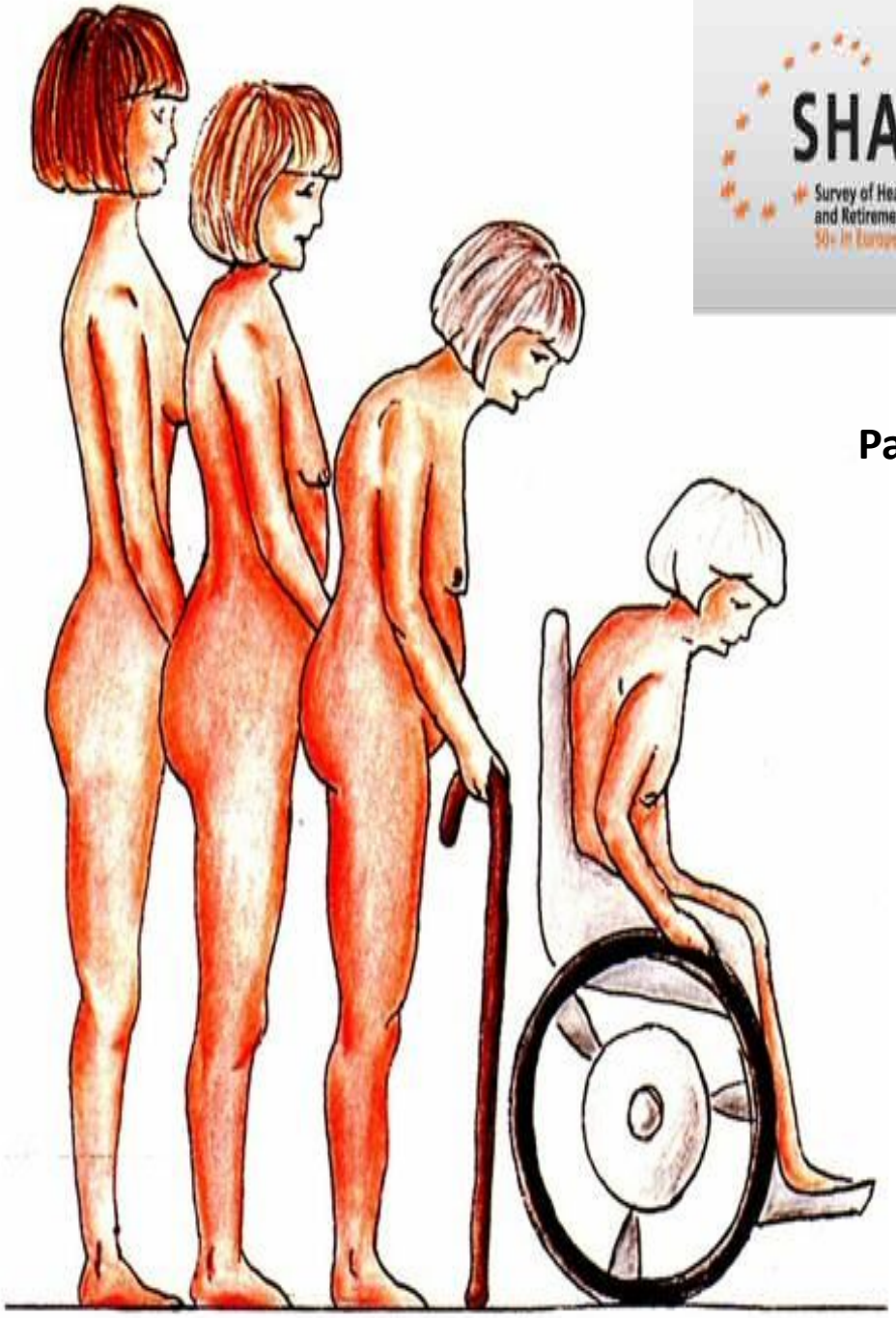
Uno stato dinamico che colpisce un individuo che sperimenta perdite in uno o più domini funzionali (fisico, psichico, sociale), causate dall'influenza di più variabili che aumentano il rischio di risultati avversi per la salute

Gobbens e Coll. (2010)




## Paziente poco compliante





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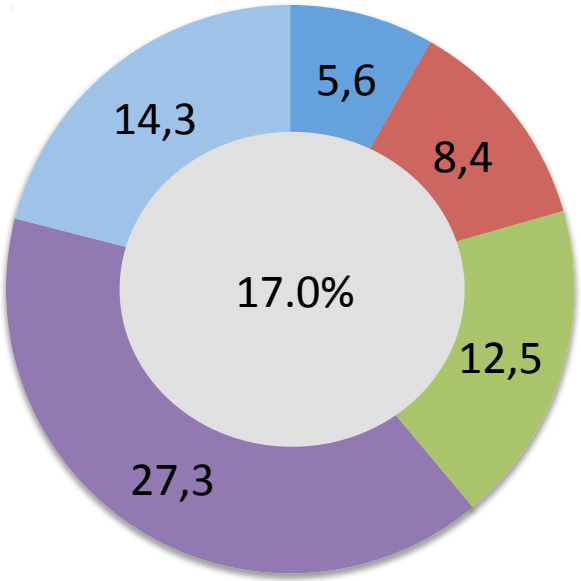
## Paziente Fragile



http://www.agenziafarmaco.gov.it

Comunicato Stampa 313, 31/07/2013

## Studio AIFA fotografa correttezza cure nella popolazione anziana/fragile

Un anziano su due oltre i 65 anni nel nostro Paese assume dai 5 ai 9 farmaci al giorno.

I pazienti fragili aumentano il numero di farmaci assunti giornalmente di 3 principi attivi nel primo anno.

Quasi il 60% della popolazione ultra-65enne e il 50% dei pazienti fragili manifestano scarsa aderenza alle terapie.

evidence
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Hot topics

OPEN ACCESS

# La non-compliance alla terapia farmacologica: strategie diagnostico-terapeutiche

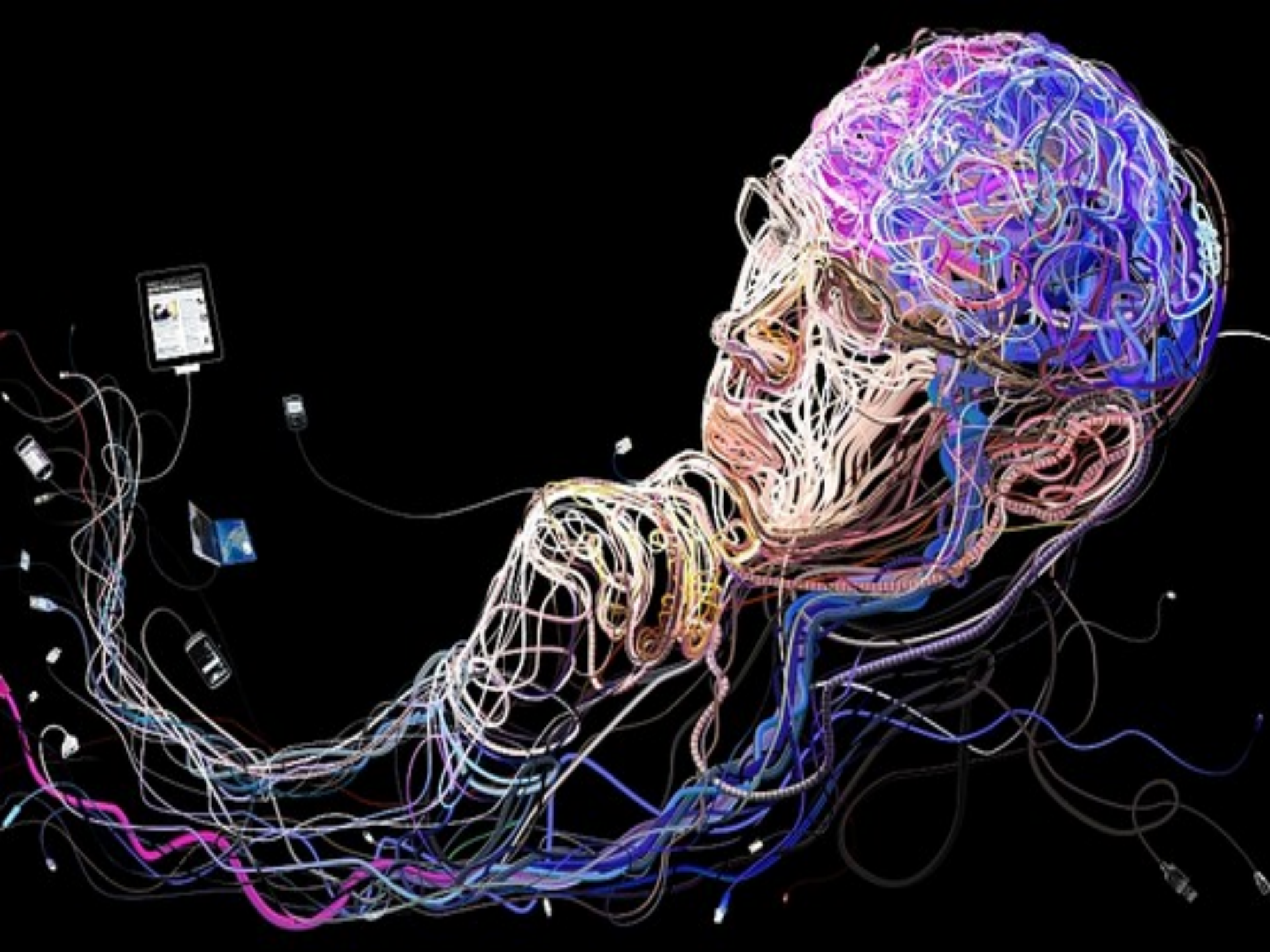
**Antonino Cartabellotta**[1*]

[1] Presidente Fondazione GIMBE

La mancata aderenza (non-compliance) di un paziente alle prescrizioni farmacologiche è oggi universalmente riconosciuta come un problema frequente che aumenta i costi dell'assistenza[1]. Negli USA, ad esempio, il 30-50% degli adulti non segue adeguatamente le prescrizioni di farmaci a lungo termine, con un costo evitabile stimato in circa 100 mld di dollari/anno. Nonostante l'ampia prevalenza del fenomeno e i costi correlati, la mancata aderenza alle prescrizioni farmacologiche non viene riconosciuta e adeguatamente trattata in una significativa percentuale di pazienti adulti in vari setting assistenziali. Secondo l'OMS "massimizzare l'efficacia degli interventi finalizzati ad aumentare la compliance può avere un impatto di gran lunga maggiore sulla salute delle popolazioni di qualunque altro progresso terapeutico".

**Box. I sei fenotipi di non-compliance alla terapia farmacologica**

1. Il paziente non è consapevole dell'importanza di seguire le prescrizioni farmacologiche per la sua salute e il suo benessere a lungo termine.
2. Il paziente è convinto che i benefici legati all'assunzione dei farmaci non siano superiori all'impegno richiesto per seguire la terapia.
3. La gestione della terapia farmacologica è troppo complessa per il paziente.
4. Il paziente non è sufficientemente vigile.
5. Il paziente ha convinzioni personali sui farmaci errate, irrazionali o conflittuali.
6. Il paziente non è convinto dell'efficacia del farmaco.



| Dispensed prescriptions Mn | | 2009 | 2010 | 2011 | 2012 | 2013 |
|---|---|---|---|---|---|---|
| **Total U.S. market** | | **3,953** | **3,995** | **4,022** | **4,139** | **4,208** |
| 1 | acetaminophen/hydrocodone | 129.4 | 132.1 | 136.7 | 136.4 | 129.2 |
| 2 | levothyroxine | 100.2 | 103.2 | 104.7 | 112.2 | 115.2 |
| 3 | lisinopril | 83.0 | 87.6 | 88.8 | 99.1 | 101.5 |
| 4 | metoprolol | 76.9 | 76.6 | 76.3 | 82.6 | 83.9 |
| 5 | simvastatin | 84.1 | 94.4 | 96.8 | 89.3 | 79.1 |
| 6 | amlodipine | 52.1 | 57.8 | 62.5 | 69.1 | 74.0 |
| 7 | metformin | 53.8 | 57.0 | 59.1 | 67.8 | 72.8 |
| 8 | omeprazole | 45.6 | 53.5 | 59.4 | 66.6 | 70.7 |
| 9 | atorvastatin | 51.7 | 45.3 | 43.3 | 55.5 | 68.4 |
| 10 | albuterol | 54.5 | 55.1 | 56.9 | 61.2 | 63.5 |
| 11 | amoxicillin | 52.8 | 52.4 | 53.8 | 52.8 | 54.2 |
| 12 | hydrochlorothiazide | 47.9 | 47.8 | 48.1 | 51.2 | 50.2 |
| 13 | alprazolam | 45.3 | 47.7 | 49.1 | 49.5 | 49.6 |
| 14 | azithromycin | 54.7 | 53.6 | 56.2 | 54.6 | 48.6 |
| 15 | fluticasone | 30.1 | 34.8 | 38.4 | 42.1 | 45.3 |
| 16 | furosemide | 43.8 | 43.6 | 42.3 | 44.1 | 45.0 |
| 17 | gabapentin | 25.7 | 29.6 | 33.4 | 38.6 | 43.9 |
| 18 | sertraline | 34.8 | 36.2 | 37.6 | 39.7 | 41.7 |
| 19 | zolpidem | 42.7 | 43.7 | 44.6 | 44.0 | 41.5 |
| 20 | tramadol | 25.5 | 28.0 | 33.9 | 39.3 | 41.5 |
| 21 | citalopram | 27.3 | 32.2 | 37.8 | 41.6 | 39.5 |
| 22 | prednisone | 27.8 | 28.7 | 33.7 | 35.2 | 36.5 |
| 23 | acetaminophen/oxycodone | 36.7 | 37.9 | 38.8 | 38.0 | 35.9 |
| 24 | ibuprofen | 30.3 | 31.1 | 32.6 | 34.2 | 35.1 |
| 25 | pravastatin | 17.2 | 20.2 | 23.9 | 33.3 | 34.7 |

Source: IMS Health, National Prescription Audit, Dec 2013

www.imshealth.com

CLINICAL REVIEW

For the full versions of these articles see bmj.com

# Management of hypothyroidism in adults

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Cite this as: *BMJ* 2008;337:a801
doi:10.1136/bmj.a801

Hypothyroidism is one of the commonest chronic disorders in Western populations. In the United Kingdom, the annual incidence of primary hypothyroidism in women is 3.5 per 1000 and in men 0.6 per 1000.[1] During 2006 12 million prescriptions for levothyroxine (50 µg or 100 µg tablets) were dispensed in England, equivalent to about 1.6 million people taking long term thyroid replacement therapy, about 3% of the population.[2] The management of hypothyroidism is generally considered straightforward and is mostly carried out in primary care in the UK. Cross sectional surveys of patients taking levothyroxine have, however, shown that between 40% and 48% are either over-treated or under-treated.[3 4] Furthermore, a to a severe impairment of consciousness, termed "myxoedema coma" (box 2). Advanced presentations of hypothyroidism are rarely seen nowadays in developed countries.

## How to diagnose hypothyroidism?

The diagnosis of primary hypothyroidism is confirmed by an increase in the serum thyroid stimulating hormone concentration above the upper limit of the reference range. Adults presenting with symptomatic hypothyroidism often have a thyroid stimulating hormone level in excess of 10 mU/l, coupled with a reduction in the serum free or total thyroxine concentration below the reference range. Some adults

BMJ. 28:337-348, 2008

Best Practice & Research Clinical Endocrinology & Metabolism 23 (2009) 781–792

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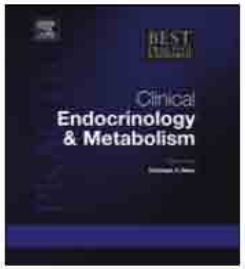
journal homepage: www.elsevier.com/locate/beem




8

# Conditions and drugs interfering with thyroxine absorption

Llanyee Liwanpo, MD, Doctor *, Jerome M. Hershman, MD, Professor

*Department of Endocrinology, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA*

Compliance

Politerapia

Conditions and medications that may affect absorption of levothyroxine.

| Foods | Medical conditions | Drugs |
|---|---|---|
| Food intake | Jejunoileal bypass or other bowel resection | Cholestyramine |
| Dietary fiber | Inflammatory bowel disease | Colesevelam |
| Espresso coffee | Celiac disease | Ferrous sulfate |
| | Lactose intolerance | Sucralfate |
| | *H. pylori* infection | Calcium carbonate |
| | Chronic gastritis of the stomach body | Aluminum hydroxide |
| | | Sevelamer hydrochloride |
| | | Lanthanum carbonate |
| | | Raloxifene |
| | | Proton pump inhibitors |
| | | Orlistat |

# Subclinical hyperthyroidism





**Mortality** — Although subclinical hyperthyroidism has been associated with several cardiovascular risk factors, it is unknown whether there is an increase in mortality. In a meta-analysis of five population-based studies examining the association between subclinical hyperthyroidism (TSH less than 0.3 to 0.5 mU/L) and cardiovascular and all-cause mortality, the risk for all-cause and cardiovascular mortality was not significant (RRs 1.12, 95% CI 0.89-1.42 and 1.19, 95% CI 0.81-1.76, respectively) [30]. In contrast, another meta-analysis showed a significantly increased risk of all-cause mortality (HR 1.41, 95% CI 1.12-1.79) [31]. In a mathematical model designed a priori to explore mortality risk, the excess mortality after diagnosis of subclinical hyperthyroidism depended upon age, with an increase beyond the age of 60 years.

The meta-analyses included patients with both exogenous and endogenous subclinical hyperthyroidism. Serum T3 levels are higher in patients with endogenous than exogenous subclinical hyperthyroidism, and this may confer a higher mortality risk [25]. In some [32,33], but not all [20,34,35], studies evaluating patients with endogenous subclinical hyperthyroidism separately, subclinical hyperthyroidism was associated with an increase in all cause and/or cardiovascular mortality.

In a study evaluating patients with exogenous subclinical hyperthyroidism separately, there was an increased risk of cardiovascular or overall mortality only in patients with fully suppressed TSH levels [36]. In this cohort study of 17,684 patients (mean age 61.6 years) taking T4 replacement therapy, TSH levels were fully suppressed (<0.03 mU/L) or low (0.04 to 0.4 mU/L) in 6 and 21 percent of patients, respectively. Compared to patients with normal TSH, patients with suppressed TSH concentrations (<0.03 mU/L) had increased cardiovascular morbidity and mortality (Adjusted HR 1.37, 95% CI 1.17-1.60), whereas those who had serum TSH levels between 0.04 and 0.4 mU/L had a smaller increase in risk that was not significant (adjusted HR 1.10 [95% CI 0.99-1.23]).

Overall, the increased risk of mortality from subclinical hyperthyroidism appears to be small, but it may increase with age and degree of TSH suppression.

**Mortality** — In some [28,29,44-46], but not all [32,47-49], studies, patients with subclinical hypothyroidism have an increased risk of cardiovascular and/or all-cause mortality. In a meta-analysis of patient level data from 11 prospective cohort studies, the risk of cardiovascular mortality, but not all-cause mortality, increased with higher concentrations of TSH and was significantly increased in participants with TSH concentrations ≥10 mU/L (HR 1.58, 95% CI 1.10-2.27) [34]. In contrast, minimal elevations of TSH (4.5 to 6.9 mU/L) were not associated with cardiovascular or all-cause mortality. In one prospective study included in the meta-analysis, elderly individuals (>85 years) in the Netherlands with untreated subclinical hypothyroidism actually had a lower rate of cardiovascular and all-cause mortality [47]. In a prospective cohort study published after the meta-analysis, elderly individuals in the United States with untreated subclinical hypothyroidism had neither increased nor decreased mortality over a median follow-up period of five years [50]. (See "Diagnosis of and screening for hypothyroidism in nonpregnant adults", section on 'Effectiveness'.)

**Non-alcoholic fatty liver disease** — In a cross-sectional study, non-alcoholic fatty liver disease (NAFLD) was correlated with serum TSH levels. Thirty and 36 percent of individuals with subclinical or overt hypothyroidism, respectively, had typical ultrasonographic findings of NAFLD (versus 20 percent of controls) while 20 and 26 percent of individuals with subclinical or overt hypothyroidism had abnormal liver enzymes [51].

**Neuropsychiatric symptoms** — Several reports suggest that subclinical hypothyroidism is associated with neuropsychiatric diseases [52-55]. However, other studies (including a large study of primary care patients in England that failed to demonstrate an association of subclinical hypothyroidism with depression, anxiety, or cognitive dysfunction) do not support this observation [10,47,56-58].

**Potential consequences**

- In three studies, increasing serum TSH concentrations within the normal range were associated with a modest increase in body weight [59-61]. (See "Etiology and natural history of obesity", section on

Arch Intern Med. 2010 Dec 13;170(22):1996-2003. doi: 10.1001/archinternmed.2010.436.

# Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial.

Bolk N[1], Visser TJ, Nijman J, Jongste IJ, Tijssen JG, Berghout A.

**Author information**

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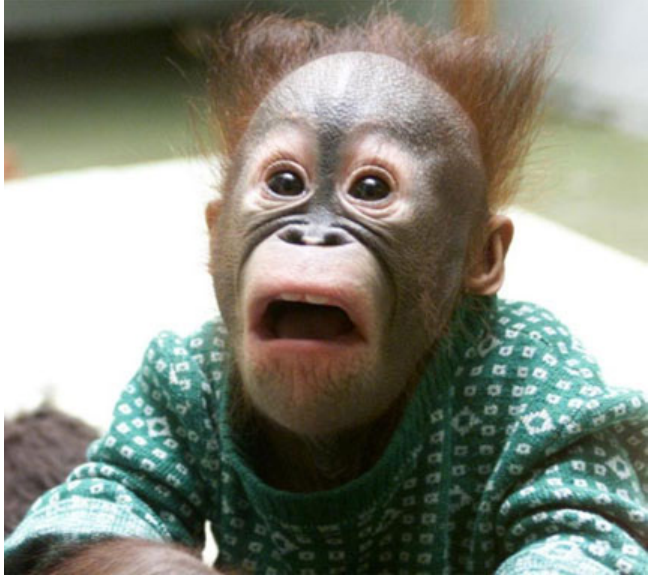
## Abstract

**BACKGROUND:** Levothyroxine sodium is widely prescribed to treat primary hypothyroidism. There is consensus that levothyroxine should be taken in the morning on an empty stomach. A pilot study showed that levothyroxine intake at bedtime significantly decreased thyrotropin levels and increased free thyroxine and total triiodothyronine levels. To date, no large randomized trial investigating the best time of levothyroxine intake, including quality-of-life evaluation, has been performed.

**METHODS:** To ascertain if levothyroxine intake at bedtime instead of in the morning improves thyroid hormone levels, a randomized double-blind crossover trial was performed between April 1, 2007, and November 30, 2008, among 105 consecutive patients with primary hypothyroidism at Maasstad Hospital Rotterdam in the Netherlands. Patients were instructed during 6 months to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Primary outcome measures were thyroid hormone levels; secondary outcome measures were creatinine and lipid levels, body mass index, heart rate, and quality of life.

**RESULTS:** Ninety patients completed the trial and were available for analysis. Compared with morning intake, direct treatment effects when levothyroxine was taken at bedtime were a decrease in thyrotropin level of 1.25 mIU/L (95% confidence interval [CI], 0.60-1.89 mIU/L, $P < .001$), an increase in free thyroxine level of 0.07 ng/dL (0.02-0.13 ng/dL; $P = .01$), and an increase in total triiodothyronine level of 6.5 ng/dL (0.9-12.1 ng/dL; $P = .02$) (to convert thyrotropin level to micrograms per liter, multiply by 1.0; free thyroxine level to picomoles per liter, multiply by 12.871; and total triiodothyronine level to nanomoles per liter, multiply by 0.0154). Secondary outcomes, including quality-of-life questionnaires (36-Item Short Form Health Survey, Hospital Anxiety and Depression Scale, 20-Item Multidimensional Fatigue Inventory, and a symptoms questionnaire), showed no significant changes between morning vs bedtime intake of levothyroxine.

**CONCLUSIONS:** Levothyroxine taken at bedtime significantly improved thyroid hormone levels. Quality-of-life variables and plasma lipid levels showed no significant changes with bedtime vs morning intake. Clinicians should consider prescribing levothyroxine intake at bedtime.



Abstract

Am J Health Syst Pharm. 2015 Mar 1;72(5):373-7. doi: 10.2146/ajhp140250.

# Alternative schedules of levothyroxine administration.

Geer M[1], Potter DM[1], Ulrich H[1].

Author information

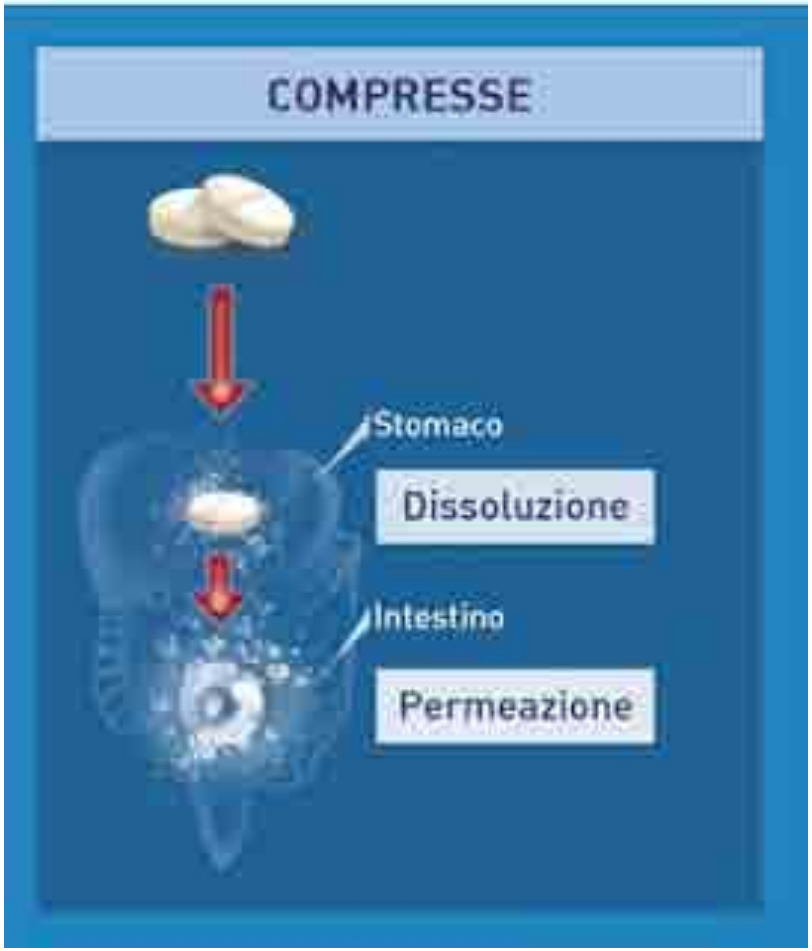
## Abstract

**PURPOSE:** Published evidence on bedtime versus prebreakfast administration of levothyroxine is reviewed.

**SUMMARY:** Because levothyroxine absorption has been shown to increase when the drug is administered to patients in a fasted state, the standard recommendation is that levothyroxine be taken one half to one hour prior to breakfast and at least four hours before or after potentially interacting drugs. However, compliance with this recommendation may be problematic for patients with unpredictable or variable schedules. A literature search identified four published studies of bedtime levothyroxine dosing. Two of the studies demonstrated a significant decrease in levels of thyroid-stimulating hormone (TSH) with levothyroxine administration at bedtime versus 30 minutes before breakfast, one study showed an increase in TSH when levothyroxine was taken at bedtime versus one hour before breakfast, and one study found no significant differences in TSH levels or other thyroid function monitoring limitations with bedtime versus standard dosing in subjects naive to levothyroxine therapy. The inconsistent study findings may be attributable to a number of variables, including dietary differences among the study populations, the use of potentially interacting supplements in one study, and variable intervals between levothyroxine administration and food intake. Neither dosing method correlated with substantial changes in assessments of quality of life or symptom severity; in two of the studies, patients indicated a preference for bedtime levothyroxine administration.

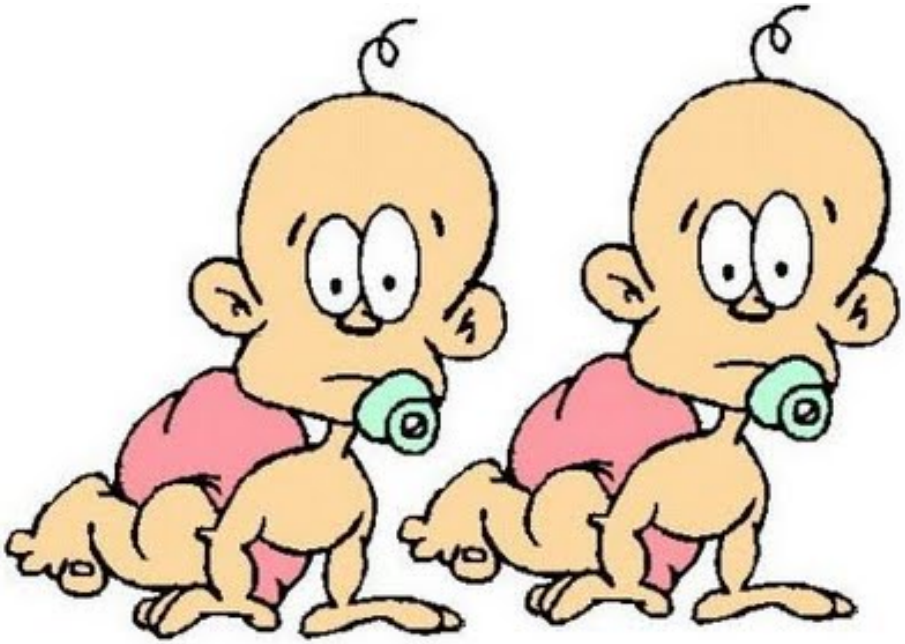
**CONCLUSION:** Based on the available literature, bedtime administration of levothyroxine is an option for patients with hypothyroidism who want to avoid taking their medication with food.

**Dal 2012……**



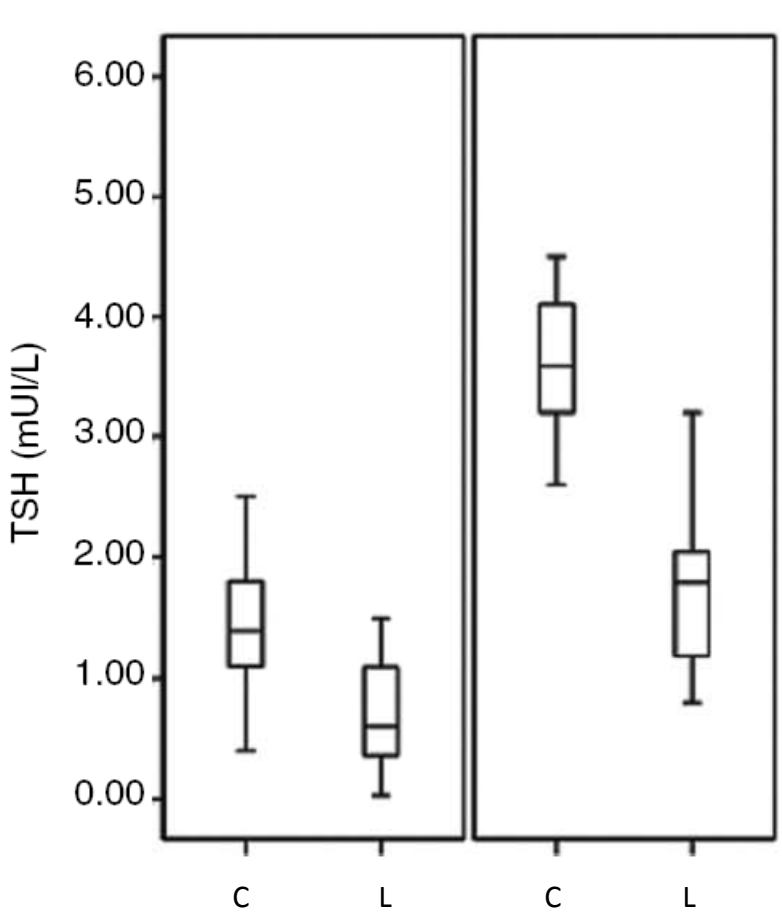

Dopo somministrazione orale il 60-90% di LT4 viene assorbita nell'intestino tenue. La fase di dissoluzione, direttamente correlata al pH gastrico, è elemento chiave per cui la terapia in compresse deve essere somministrata a stomaco vuoto la mattina a digiuno almeno 30 minuti prima di fare colazione.


I farmaci in forma liquida non necessitano della fase di dissoluzione, si miscelano direttamente con I fluidi gastrointestinali, rendendosi subito disponibili, anche in casi di patologie come la celiachia e l'intolleranza al lattosio. Le soluzioni liquide, inoltre, garantiscono una migliore permeazione del principio attivo.




WWW.JPERGRAFANDO.IT

# 24 pazienti in terapia sostitutiva in compresse sostituiti con stesso dosaggio in formulazione liquida



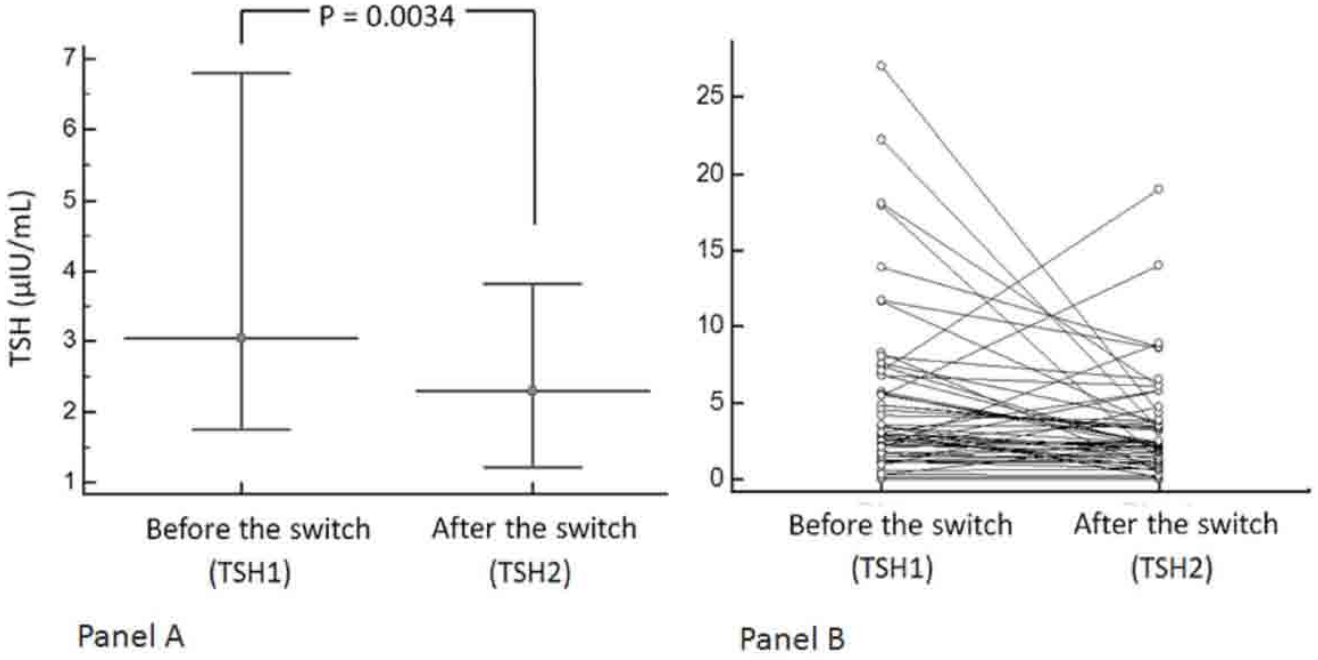

Cappelli C, personal data

Original Article EP13418.OR

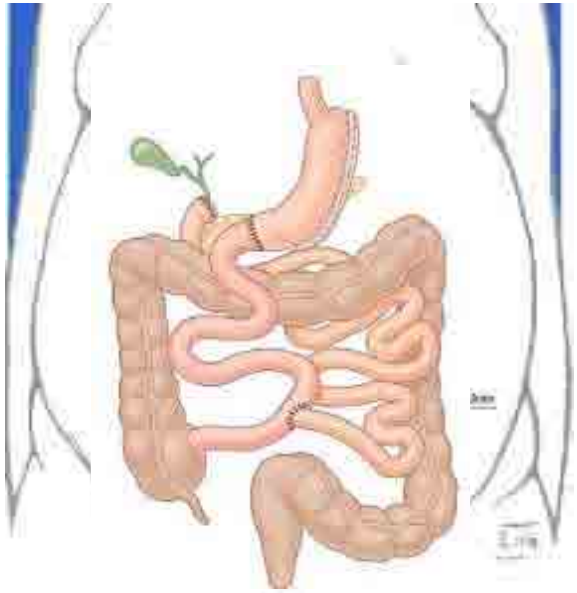
# COMPARISON OF TSH LEVELS WITH LIQUID FORMULATION VERSUS TABLET FORMULATIONS OF LEVOTHYROXINE IN THE TREATMENT OF ADULT HYPOTHYROIDISM.

Running title: LT4 tablets versus oral solution

*Davide Brancato, MD, Alessandro Scorsone, MD, Gabriella Saura, MD, Lidia Ferrara, MD, Anna Di Noto, MD, Vito Aiello, MD, Mattia Fleres, MD, Vincenzo Provenzano, MD.*




**Conclusion**. Our study confirms that LT4-OS could have an increased absorption rate in comparison to LT4 tablets, especially when other factors interfering with LT4 absorption are present.



Diversione biliopancreatica

Thyroid parameters measured at the indicated times in four patients who underwent bariatric surgery between 2009 and 2011. Patients were receiving oral L-T4 in either tablet or liquid form as indicated

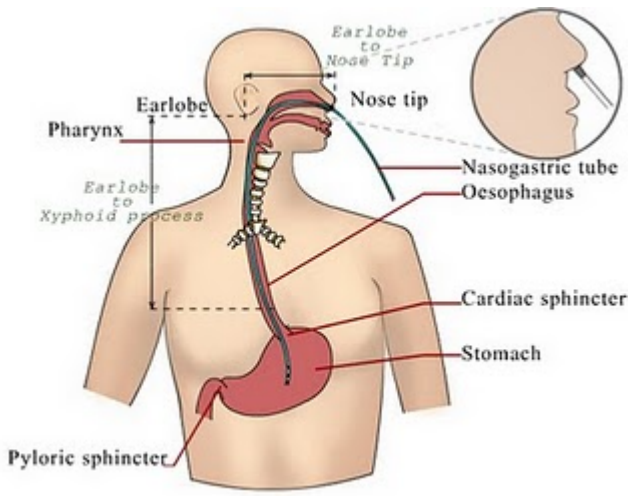
| | Before surgery L-T4 in tablet form | | | | 12 Months after surgery L-T4 in tablet form | | | | 14 Months after surgeryL-T4 in liquid form | | | | 17 Months after surgery L-T4 in tablet form | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | L-T4 (μg) | TSH | fT4 | fT3 | L-T4 (μg) | TSH | fT4 | fT3 | L-T4 (μg) | TSH | fT4 | fT3 | L-T4 (μg) | TSH | fT4 | fT3 |
| 1 | 200 | 4.2 | 12.7 | 3.1 | 200 | 18.1 | 10.4 | 2.9 | 200 | 1.5 | 12.9 | 3.8 | 200 | 36.7 | 9.8 | 3.0 |
| 2 | 150 | 3.1 | 12.9 | 3.3 | 150 | 12.1 | 10.2 | 3.2 | 150 | 1.9 | 13.5 | 4.0 | 150 | 24.7 | 10.4 | 3.2 |
| 3 | 200 | 3.9 | 11.7 | 3.7 | 200 | 20.4 | 10.2 | 3.3 | 200 | 0.6 | 13.5 | 3.2 | 200 | 17.7 | 10.2 | 3.1 |
| 4 | 150 | 3.6 | 10.9 | 3.2 | 150 | 17.2 | 11.0 | 2.8 | 150 | 2.4 | 11.9 | 3.2 | 150 | 15.3 | 10.1 | 3.1 |

*L-T4* levothyroxine, *TSH* thyrotropin, *fT4* free tyroxine, *fT3* free triiodothyronin

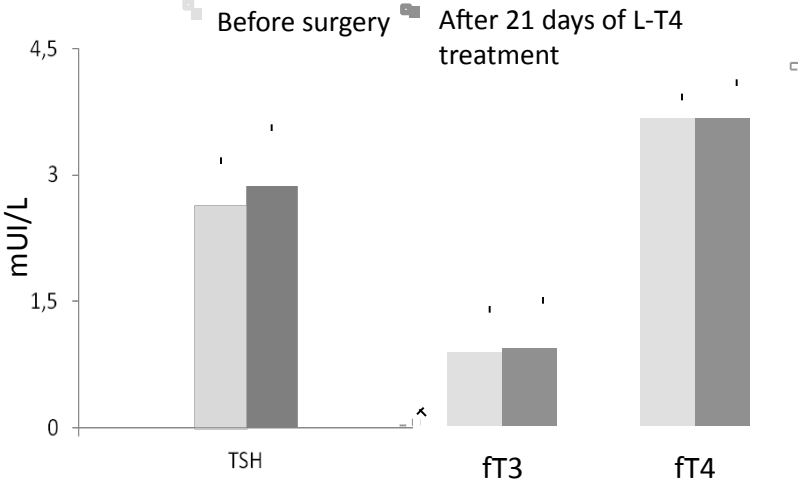
In summary, we report four patients submitted to bariatric surgery, in whom oral liquid l-thyroxine induced a reversible normalisation of thyrotropin levels. It is likely that patients affected by condition that impair l-T4 absorption (e.g., bariatric surgery) could benefit from a liquid formulation.

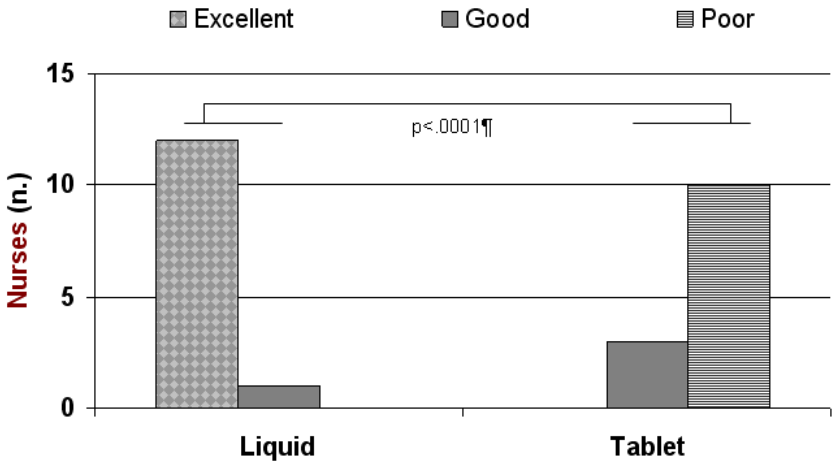
Pirola I et al, Obes Surg. 2013; 23: 1493–1496.

# Comparison between liquid and tablet levothyroxine formulations in patients treated through enteral feeding tube.




| | Patients treated with L-T4 *Tablet form* | Patients treated with L-T4 in *Liquid form* | P value |
|---|---|---|---|
| Patients (n.) | 10 | 10 | - |
| Gender (M/F) | 9/1 | 9/1 | Ns |
| Age (yrs) | 68±5.8 | 69.1±5.1 | Ns |
| BMI (Kg/cm$^2$) | 23±2.1 | 23.1±1.9 | Ns |
| TSH (mUI/L) | 2.50±1.18 | 2.79±1.03 | Ns |
| fT4 (pg/mL) | 12.31±1.89 | 12.68±2.68 | Ns |
| fT3 (pg/mL) | 3.21±0.56 | 3.09±0.62 | Ns |




Pirola I et al, J Endocrinol Invest. 2014 Jun;37(6):583-7

# Oral liquid levothyroxine treatment at breakfast: a mistake?

**Carlo Cappelli, Ilenia Pirola, Elena Gandossi, Annamaria Formenti** and **Maurizio Castellano**

Endocrine and Metabolic Unit, Clinica Medica, Department of Clinical and Experimental Sciences, University of Brescia, c/o 1^ Medicina Spedali Civili di Brescia, Piazzale Spedali Civili no. 1, 25100 Brescia, Italy

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cappelli@med.unibs.it

**Table 1** Clinical and biochemical parameters of patients at recruitment.

| | **Group A** ($n=41$) | **Group B** ($n=13$) | ***P* value** |
|---|---|---|---|
| Age (years) | 48.7±11.1 | 51.7±12.6 | 0.413 |
| L-$T_4$ dosage (μg/day) | 76.9±16.1 | 71.9±17.8 | 0.375 |
| TSH (mIU/l) | 2.3±1.1 | 2.9±0.9 | 0.056 |
| $fT_4$ (pg/ml) | 12.3±2.4 | 12.5±2.4 | 0.850 |
| $fT_3$ (pg/ml) | 3.4±0.6 | 3.4±0.5 | 0.734 |

*P* values based on ANOVA.

**Table 2** Thyroid profile of patients consuming L-$T_4$ at breakfast and after 3 and 6 months of changing the time of consumption 30 min before breakfast.

| | **Group A** ($n=41$) | | | | **Group B** ($n=13$) | | | |
|---|---|---|---|---|---|---|---|---|
| | At recruitment[a] | 3 months[b] | 6 months[b] | *P* | At recruitment[a] | 3 months[b] | 6 months[b] | *P* |
| TSH (mIU/l) | 2.3±1.1 | 2.3±1.1 | 2.3±1.0 | 0.939 | 2.9±0.9 | 2.9±0.9 | 2.8±0.9 | 0.323 |
| $fT_4$ (pg/ml) | 12.2±2.5 | 12.3±2.5 | 12.3±2.0 | 0.479 | 12.9±2.0 | 12.5±2.5 | 12.3±2.3 | 0.208 |
| $fT_3$ (pg/ml) | 3.4±0.6 | 3.3±0.6 | 3.2±0.6 | 0.079 | 3.4±0.7 | 3.5±0.6 | 3.5±0.4 | 0.615 |

*P* values based on ANOVA.
[a]Patients consuming L-$T_4$ with breakfast.
[b]After changing the time of L-$T_4$ consumption 30 min before breakfast.

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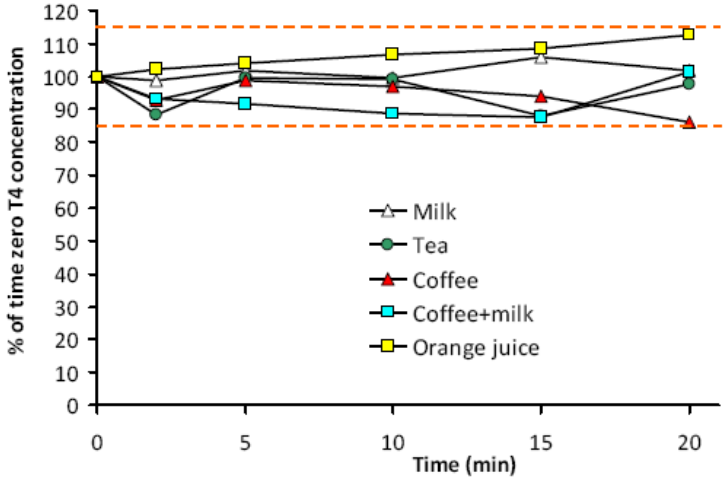
*Article*

# Oral Liquid Formulation of Levothyroxine Is Stable in Breakfast Beverages and May Improve Thyroid Patient Compliance

**Alberto Bernareggi [1,*], Elia Grata [2], Maria Teresa Pinorini [2] and Ario Conti [2]**

**Figure 3.** Graphical representation of mean percent variation of T4 concentration as a function of time with respect to time zero concentration for all tested beverages. Dashed lines indicate the acceptance limits of ±15% of time zero concentrations.

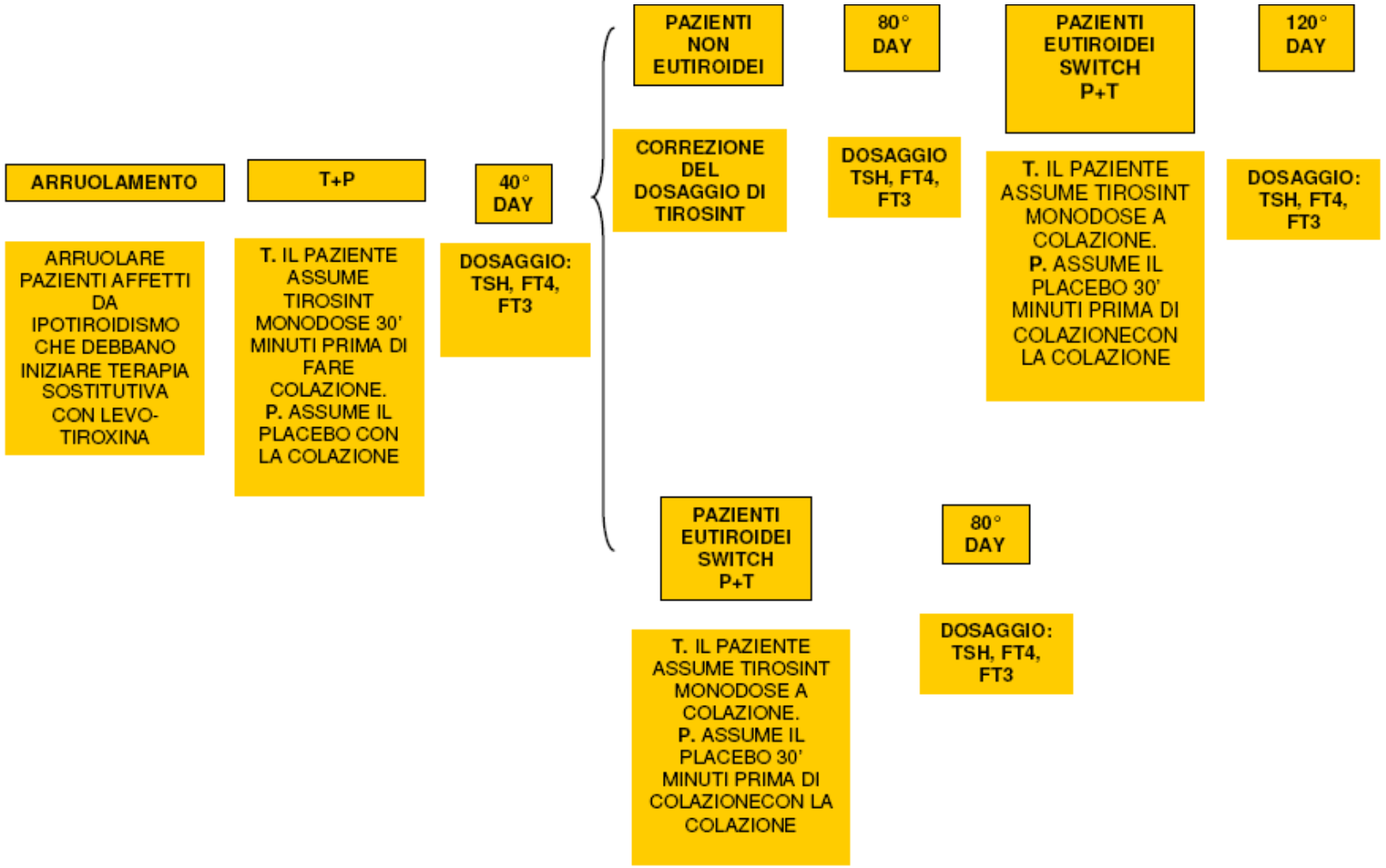



## 4. Conclusions

The results of the study demonstrated that T4 is stable in all beverages after 20 min incubation. Demonstration of T4 stability is a prerequisite for a thorough evaluation of the effect of breakfast beverages on the bioavailability of T4 given as oral solution and for a better understanding of the reasons underlying a decreased T4 bioavailability administered as solid formulations.

**STUDIO PROSPETTICO IN CIECO SULLE CARATTERISTICHE DI ASSORBIMENTO DI LEVO-TIROXINA SOLUZIONE ORALE (Tirosint® soluzione orale monodose) IN PAZIENTI AFFETTI DA IPOTIROIDISMO**

## "TICO" Study



| | ALL PATIENTS | SEQUENCE AT=>BEFORE | SEQUENCE BEFORE=>AT | P value |
|---|---|---|---|---|
| N. of patients | 77 | 38 | 39 | |
| Sex (female/male) | 64/13 | 32/6 | 32/7 | NS |
| Age (yrs) | 45.4±13.7 | 46.2±14.1 | 44.8±13.4 | NS |
| BMI | 24.2±4.7 | 24.1±4.1 | 24.3±4.6 | NS |
| Hashimoto thyroiditis | 66 | 33 | 33 | NS |
| Total thyroidectomy | 11 | 5 | 6 | |
| TSH (mUI/L) | 16.7 (8.13-87.1) | 15.1 (8.13-33.2) | 18.3 (10.1-87.1) | NS |
| fT4 (pg/mL) | 11.2 (5.3-17.5) | 11.0 (5.7-17.5) | 11.4 (5.3-16.1) | NS |
| fT3 (pg/mL) | **3.0 (2.1-4.4)** | **2.9 (2.1-4.4)** | **3.1 (2.1-4.2)** | NS |

| | ALL PATIENTS (n=77) | | |
|---|---|---|---|
| | L-T4 AT BREAKFAST | L-T4 BEFORE BREAKFAST | P value |
| TSH | 2.6±1.8 | 2.6±1.4 | 0.960 |
| fT4 | 10.6±1.4 | 10.4±1.2 | 0.074 |
| fT3 | 2.8±0.3 | 2.8±0.3 | 0.562 |
| | | | |
| | SEQUENCE AT=>BEFORE (n=38) | | |
| | L-T4 AT BREAKFAST | L-T4 BEFORE BREAKFAST | |
| TSH | 2.3±1.3 | 2.4±1.5 | 0.574 |
| fT4 | 10.7±1.4 | 10.4±1.3 | 0.025 |
| fT3 | 2.8±0.3 | 2.8±0.3 | 0.445 |
| | | | |
| | SEQUENCE BEFORE =>AT (n=39) | | |
| | L-T4 AT BREAKFAST | L-T4 BEFORE BREAKFAST | |
| TSH | 2.9±2.2 | 2.8±1.3 | 0.672 |
| fT4 | 10.3±1.5 | 10.4±1.3 | 0.860 |
| fT3 | 2.7±0.3 | 2.7±0.3 | 1.000 |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CLINICAL REVIEW

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# Management of hypothyroidism in adults

Bijay Vaidya,[1] Simon H S Pearce[2]

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Cite this as: *BMJ* 2008;337:a801
doi:10.1136/bmj.a801

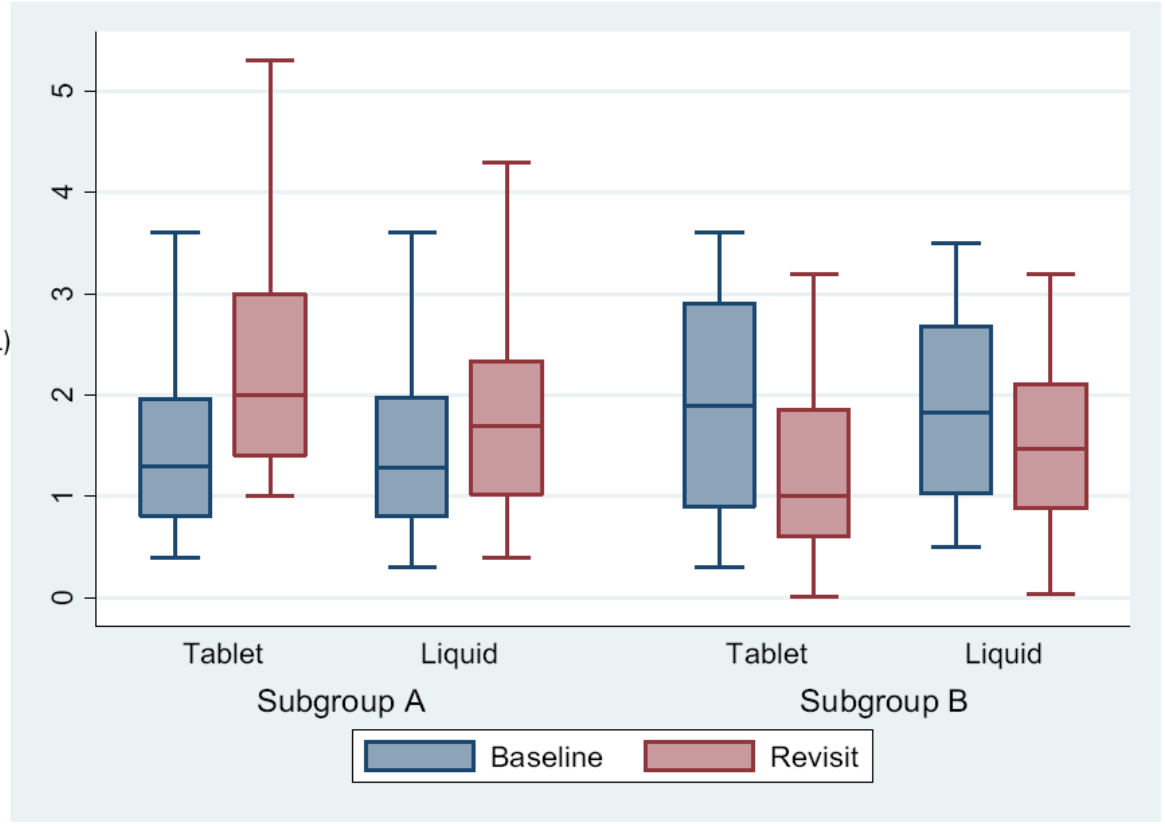
Hypothyroidism is one of the commonest chronic disorders in Western populations. In the United Kingdom, the annual incidence of primary hypothyroidism in women is 3.5 per 1000 and in men 0.6 per 1000.[1] During 2006 12 million prescriptions for levothyroxine (50 µg or 100 µg tablets) were dispensed in England, equivalent to about 1.6 million people taking long term thyroid replacement therapy, about 3% of the population.[2] The management of hypothyroidism is generally considered straightforward and is mostly carried out in primary care in the UK. Cross sectional surveys of patients taking levothyroxine have, however, shown that between 40% and 48% are either over-treated or under-treated.[3 4] Furthermore, a to a severe impairment of consciousness, termed "myxoedema coma" (box 2). Advanced presentations of hypothyroidism are rarely seen nowadays in developed countries.

## How to diagnose hypothyroidism?

The diagnosis of primary hypothyroidism is confirmed by an increase in the serum thyroid stimulating hormone concentration above the upper limit of the reference range. Adults presenting with symptomatic hypothyroidism often have a thyroid stimulating hormone level in excess of 10 mU/l, coupled with a reduction in the serum free or total thyroxine concentration below the reference range. Some adults

BMJ. 28:337-348, 2008

# Levothyroxine Liquid Solution Versus Tablet for Replacement Treatment in Hypothyroid Patients.




Conclusions. The use of L-thyroxine liquid formulation compared to tablet resulted in a significantly higher number of hypothyroid patients who maintained the euthyroid state in a 12 months of follow up, and a reduced variability in TSH values.

Negro N et al. Endocr Pract, 2014, in press

European Geriatric Medicine xxx (2014) xxx–xxx

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Research paper

# Thyroid hormonal profile in elderly patients treated with two different levothyroxine formulations: A single institute survey

C. Cappelli *, I. Pirola, L. Daffini, E. Gandossi, B. Agosti, M. Castellano

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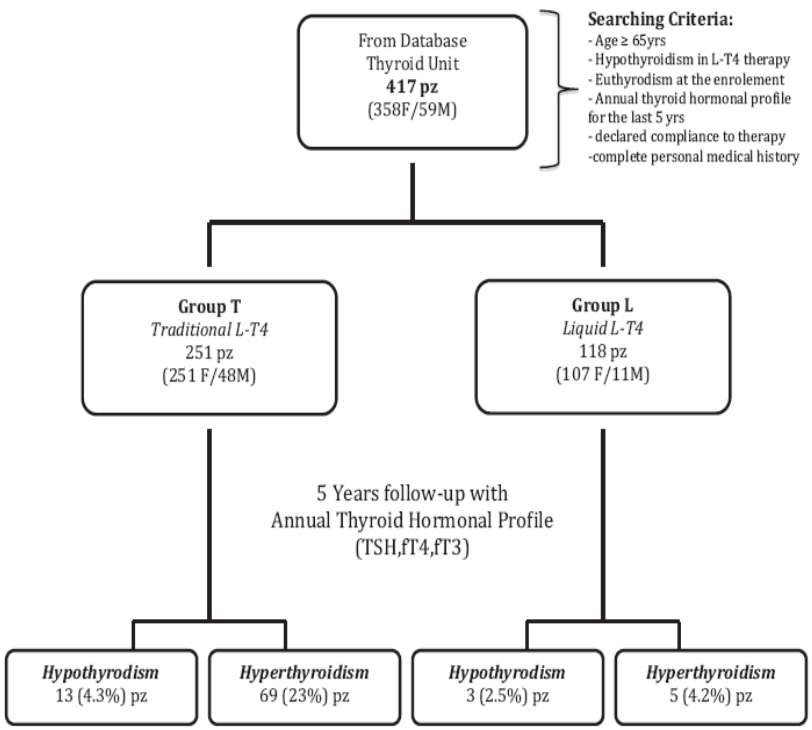



**Fig. 1.** Schematic diagram of the study design and data collection.

**Table 2**
Logistic regression analysis of developing subclinical or hyperthyroidism in the study population.

| | Odds ratio (95% CI) | *P* value |
|---|---|---|
| Age (yrs) | 1.00 (0.96–1.05) | NS |
| Gender (female) | 1.51 (0.76–3.01) | NS |
| BMI (kg/cm$^2$) | 0.54 (0.25–1.10) NS | NS |
| Thyroid disorder (Hashimoto thyroiditis) | 0.72 (0.36–1.56) NS | NS |
| Concomitant drugs therapy | 0.56 (0.25–1.10) | NS |
| Levothyroxine (tablets) | 2.35 (1.14–4.83) | 0.021 |

Arzneimittelforschung. 2012 Dec;62(12):631-6. doi: 10.1055/s-0032-1329951. Epub 2012 Nov 15.

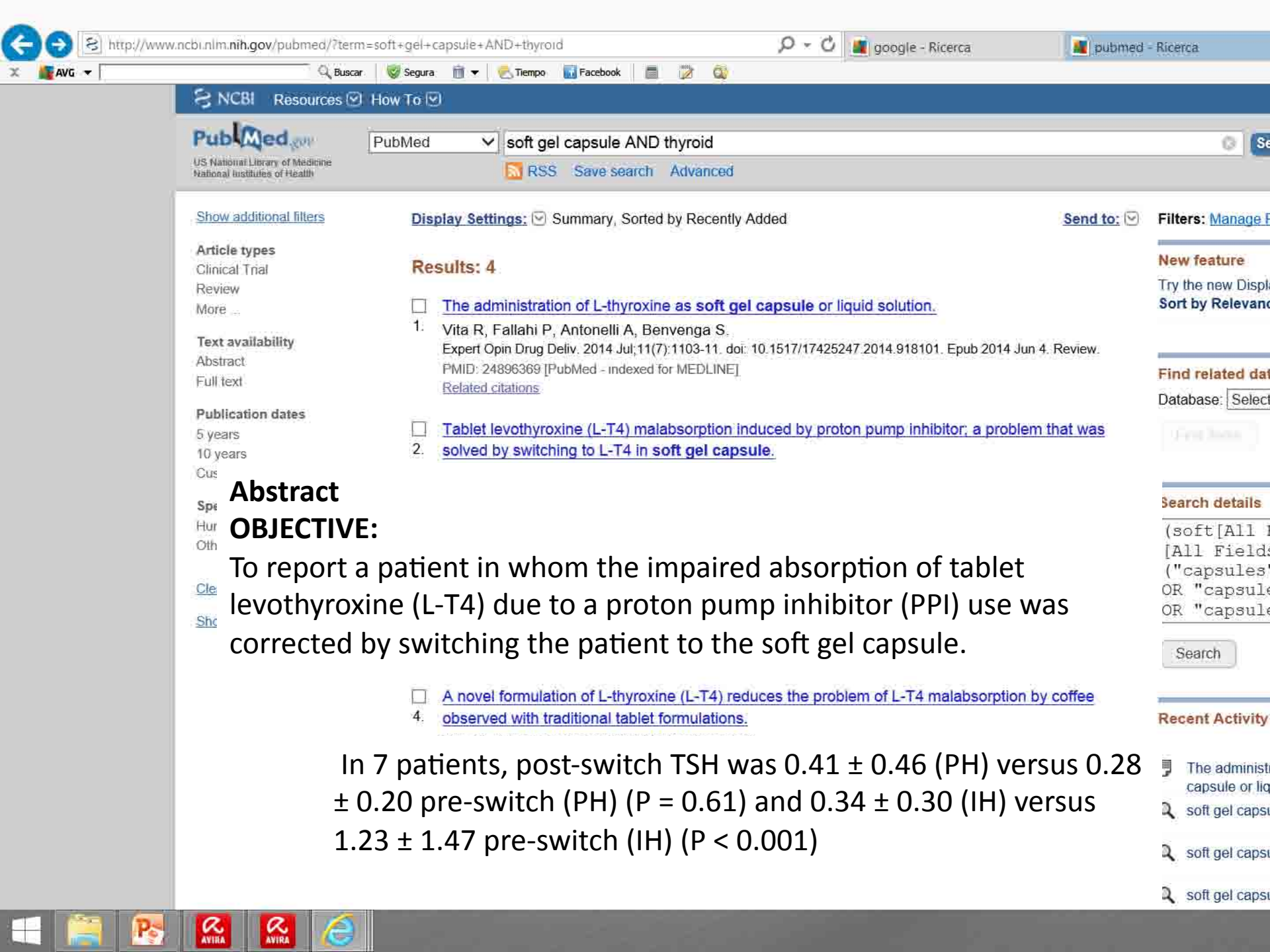
# Pharmacokinetics and potential advantages of a new oral solution of levothyroxine vs. other available dosage forms.

C. S. Yue[1], C. Scarsi[2], M. P. Ducharme[1]

[1]Faculté de pharmacie, Université de Montréal, Montreal, Quebec, Canada
[2]R&D Department, IBSA Institut Biochimique SA, Pambio-Noranco, Switzerland

## Abstract

To better understand the pharmacokinetics and potential advantages of a levothyroxine oral solution vs. tablets and soft gel capsules.4 randomized, 2-treatment, single-dose (600 mcg levothyroxine), 2-way crossover bioequivalence studies in 84 healthy subjects were analyzed. Samples were collected before dosing and until 48-72 h post-dose to calculate noncompartmental baseline-adjusted pharmacokinetic parameters: maximum concentration, time to maximum concentration, and area-under-the-concentration-time-curve from 0 to 48 h and from 0 to 2 h.Mean pharmacokinetic parameters (±standard deviation) for tablets, capsules and solution, respectively, were: area-under-the-concentration-time-curve from 0 to 2 h (ng*h/mL)=68.4±32.8, 64.4±24.4, 99.1±22.7; area-under-the-concentration-time-curve from 0 to 48 h (ng*h/mL)=1 632±424, 1 752±445, 1 862±439; maximum concentration (ng/mL)=67.6±20.9, 68.0±15.9, 71.4±16.0; time of maximum concentration (hours)=2.25±0.99, 2.38±1.58, 1.96±1.07. Overall rate and extent of exposure were not statistically different between formulations, but a faster onset of absorption for the solution was suggested (greater area-under-the-concentration-time-curve from 0 to 2 h and faster time to maximum concentration by an average of 30 min).Levothyroxine rate and extent of exposure are similar between tested formulations. The solution appears however to reach systemic circulation quicker as dissolution is not needed before absorption starts. The solution's greater early exposure and a faster time to maximal concentration of around 30 min may be of benefit to minimize drug-food interactions and deserves further investigations.


http://www.ncbi.nlm.nih.gov/pubmed/?term=soft+gel+capsule+AND+thyroid
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Display Settings: Summary, Sorted by Recently Added
Send to:
Filters: Manage
Article types
Clinical Trial
Review
More ...
Text availability
Abstract
Full text
Publication dates
5 years
10 years
Results: 4
1. The administration of L-thyroxine as soft gel capsule or liquid solution.
Vita R, Fallahi P, Antonelli A, Benvenga S.
Expert Opin Drug Deliv. 2014 Jul;11(7):1103-11. doi: 10.1517/17425247.2014.918101. Epub 2014 Jun 4. Review.
PMID: 24896369 [PubMed - indexed for MEDLINE]
Related citations
2. Tablet levothyroxine (L-T4) malabsorption induced by proton pump inhibitor; a problem that was solved by switching to L-T4 in soft gel capsule.
Abstract
OBJECTIVE:
To report a patient in whom the impaired absorption of tablet levothyroxine (L-T4) due to a proton pump inhibitor (PPI) use was corrected by switching the patient to the soft gel capsule.
4. A novel formulation of L-thyroxine (L-T4) reduces the problem of L-T4 malabsorption by coffee observed with traditional tablet formulations.
In 7 patients, post-switch TSH was 0.41 ± 0.46 (PH) versus 0.28 ± 0.20 pre-switch (PH) (P = 0.61) and 0.34 ± 0.30 (IH) versus 1.23 ± 1.47 pre-switch (IH) (P < 0.001)
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European
Thyroid Journal


Eur Thyroid J 2014;3(suppl 1):73–226
DOI: 10.1159/000365244
Published online: August 15, 2014

# 38th Annual Meeting of the European Thyroid Association

## Abstracts

Santiago de Compostela, Spain
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**P146**

## ORAL SOLUTION (OS) LEVOTHYROXINE (LT4) PERMITS TO REACH TARGET TSH LEVELS IN PATIENTS WHO TAKE TWO OR MORE DRUGS KNOWN TO IMPAIR TEH INTESTINAL ABSORTPION OF LT4

Roberto Vita1, Giovanna Saraceno1, Francesco Trimarchi1, Salvatore Benvenga1
1Endocrinology, Department of Clinical & Experimental Medicine, University of Messina

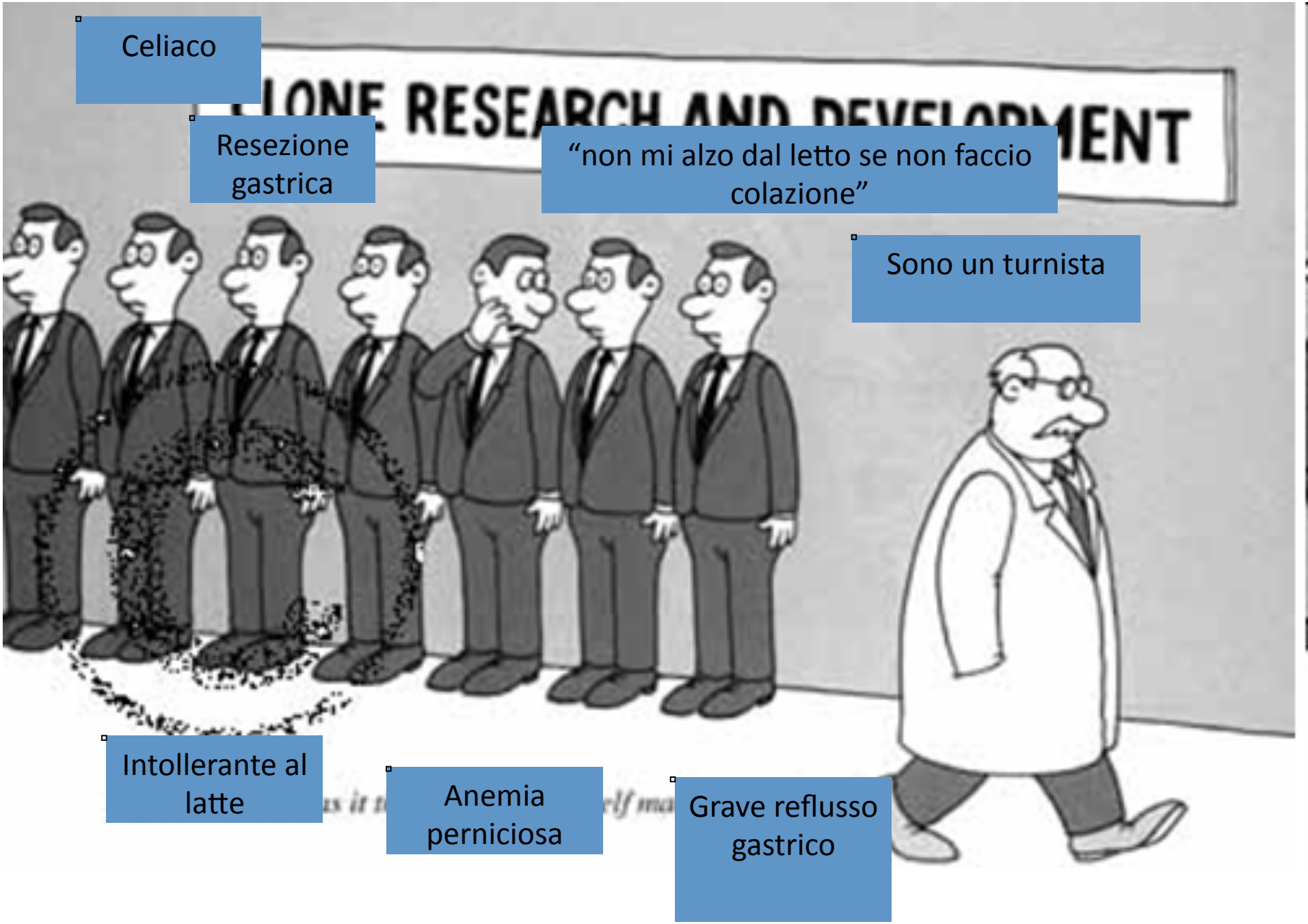
**Objectives:** To challenge the better absorption profile of a liquid formulation (OS) of L-T4 over tablet L-T4 by verifying whether OS would correct the tablet L-T4 malabsorption caused by the co-ingestion of two or more interfering drugs.

**Methods:** Thus far we have enrolled 11 patients who took tablet L-T4 either for replacement (REP group, n = 5) or for TSH suppression (SUP group, n = 6) and had serum TSH above target because they were also taking at least two of: proton-pump inhibitors (n = 9), calcium carbonate (n = 6), ferrous sulfate (n = 5), sevelamer (n = 4), magnesium/aluminum hydroxide (n = 1), sodium alginate (n = 1). We switched the tablet with the OS (Tirosint® soluzione orale, IBSA Italia s.r.l.), while maintaining the same daily dose, and checked serum TSH (mU/L) at least twice, eight weeks apart. Data are m±SD. Statistics is based on Wilcoxon test and Fisher s exact test.

**Results:** In the REP group, serum TSH was lower under the OS compared to the tablet (2.7±1.1 vs. 5.8±3.2, P = 0.004). The rate of TSH values 4.12 or 2.5 was 9/9 (100%) or 4/9 (44.4%) under the OS, but 5/12 (41.7%, P = 0.007) or 0/12 (0%, P = 0.02) under the tablet. Target serum TSH levels ( 2.5) were achieved already at the first or second determination in 4/5 patients (80%) under the OS, but in none under the tablet (P = 0.05). In the SUP group, TSH was also lower under the OS (0.5±0.6 vs. 3.2±2.6, P < 0.0001). The rate of TSH values 0.10 was 11/24 (45.8%) under the OS, but 0/14 under the tablet (P = 0.02). Target serum TSH levels ( 0.1) were achieved already at the first or second determination in 4/6 patients (66.7%) under the OS, but in none under the tablet (P = 0.06).

**Conclusions:** In patients taking 2 drugs that interfere with L-T4 intestinal absorption, the OS ensures an absorption of L-T4 far better than the tablet.

Sig. Rossi (51 aa): TSH 21.5 mU/L, fT4 6.6 pg/mL.


Celiaco
Resezione gastrica
“non mi alzo dal letto se non faccio colazione”
Sono un turnista
Intollerante al latte
Anemia perniciosa
Grave reflusso gastrico

# CONCLUSIONI

- La terapia con L-T4 è sicura e maneggevole, ma deve essere personalizzata non solo nel dosaggio.
- La forma liquida è di scelta nel paziente Celiaco e intollerante al lattosio.
- La forma liquida risentirebbe meno della colazione
- Il profilo tiroideo appare più stabile nel tempo con la formulazione liquida