LETTERS TO THE EDITOR

LEVOTHYROXINE BIOEQUIVALENCE

To the Editor:

The relative equivalence of levothyroxine products has been a decades-long controversy.[1,2] In the JFP Journal Club review of the study by Dong et al[3], the four tested products were claimed to be bioequivalent. The products tested however, were *not* equivalent.

The following are several points that readers should consider:

1. The 24 patients studied were a heterogeneous group and most likely had residual endogenous thyroid hormone production. The response to levothyroxine in these distinct types of hypothyroid patients may not be the same.

2. While the results of the bioequivalence calculations show that the areas under the curve of the four products are not significantly different, review of the hormone assays shows a different picture. Peak serum free thyroxine index occurred within 2 hours in 73% of patients after taking Synthroid, in 52% after taking Levoxyl, in 48% after taking the generic form from Geneva Generics, and in 48% after taking the generic from Rugby Laboratories. In assessing serum T_3 levels, Synthroid produced a more rapid and higher rise in T_3 levels than the other preparations. Based on the above data, Synthroid appears to have different absorption characteristics from the other products.

3. Serum thyrotropin (TSH) levels, the standard-of-care biochemical monitoring tool for levothyroxine therapy, while measured by the investigators, were not reported. The thyrotropin results recently have been made available.

TABLE

Changes in Serum Thyrotropin (TSH) Levels* Tested at 3-Week Intervals in 24 Women Taking Levothyroxine

Interval	Mean TSH	Hypothyroid† No. (%)	Hyperthyroid No. (%)	Abnormal TSH No. (%)
Baseline	1.4	0	0	0
Period 1	3.1	4 (19)	4 (19)	8 (38)
Period 2	2.4	3 (14)	6 (29)	9 (43)
Period 3	1.5	3 (14)	8 (38)	11 (52)
Period 4	4.3	3 (14)	8 (38)	11 (52)

*Normal TSH range is 0.5 - 4.8 mU/L.
†Data excludes three subjects with baseline low TSH values.

The mean baseline thyrotropin (normal, 0.5 to 4.8 mU/L) for the 24 subjects was 1.4. However, three of the subjects had baseline low thyrotropin values. From the mean baseline thyrotropin of 1.4, the mean values for the subsequent four periods of the study were 3.1, 2.4, 1.5, and 4.3. Of the 21 subjects who were euthyroid at baseline, 52% lost their thyroid control at some point when the product was changed (Table).

While the conclusions of the study claim bioequivalence among the four levothyroxine products studied, the results show that these products are not therapeutically interchangeable based on absorption characteristics and thyrotropin responses.

The argument for generic levothyroxine is, of course, strictly economic. Based on 1997 average wholesale prices, a 1-month supply of Synthroid 100 µg costs $6.81 compared with $2.64 for Levoxyl. However, the cost of loss of thyroid control must be considered. Changing brands likely will result in more frequent laboratory testing and use of physician resources. These expenses could easily obviate any financial savings gained by using a generic levothyroxine product.

The issue of bioequivalence and therapeutic equivalence of levothyroxine products has not been resolved. For some drugs, such as levothyroxine, therapeutic equivalence should be the most important criterion. The FDA, as well as many state legislatures, are considering adopting tighter bioequivalence requirements for "narrow therapeutic index" drugs.[4] In fact, many state boards of pharmacy already prohibit pharmacists from substituting drugs with unresolved bioequivalence issues. In addition, the FDA announced in August 1997 that because of reports of stability and potency problems, levothyroxine products will be considered new drugs, and manufacturers must obtain an approved New Drug Application within 3 years.[5]

From a purely therapeutic standpoint, clearly the best strategy is to keep patients on the same product once therapy has been stabilized.

The Journal welcomes letters to the editor. If found suitable, they will be published as space allows. Letters should be typed double spaced, should not exceed 400 words, and are subject to abridgment and other editorial changes in accordance with Journal style. All letters that reference a recently published Journal article are sent to the original authors for their reply. If no reply is published, the authors have not responded by date of publication. Send letters to Paul A. Nutting, MD, MSPH, Editor, The Journal of Family Practice, 1650 Pierce St, Denver, CO 80214. Telephone (303) 202-1543, Fax (303) 202-5136, E-mail paul.nutting@aspn.amc.org

Managed care organizations should evaluate which levothyroxine product the majority of their patients are receiving, and they should commit to continue paying for that brand. Treating clinicians should know which specific levothyroxine preparation their patients are taking and when any change in product is contemplated.

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3. Schellhase K, Ellsworth A. Levothyroxine bioequivalence [JFP Journal Club]. J Fam Pract 1997; 45:23. Comment on: Dong BJ, Hauck WW, Gambertoglio JG, et al. Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. JAMA 1997; 277:1205-13.
4. FDA position on product selection for "narrow therapeutic index" drugs [Law Notes]. Am J Health-Syst Pharm 1997; 54:1630-2.
5. Levothyroxine sodium action: Notice. Federal Register, August 15, 1997, Docket No. 97N-0134.

The preceding letter was referred to Drs Schellhase and Ellsworth, who respond as follows:

We agree with Drs Katz and Scherger that "the argument is strictly economic." Eight million patients are currently receiving thyroid replacement. Synthroid is the third most commonly prescribed drug in the United States, represents 71% of the prescriptions for levothyroxine, and has nearly 85% of this $324 million market.[1] Obviously a great deal is a stake economically. We also agree that clinicians and dispensing pharmacists should know the specific levothyroxine preparation their patients use, and we recommend monitoring with changes in formulation. But this does not justify maintaining the status quo of prescribing patterns that developed historically in favor of the more expensive drug Synthroid. We offer the following in support of our view:

1. The study patients were heterogeneous, potentially with endogenous thyroid hormone production that could account for concentration differences between products. Having subjects serve as their own control may not eliminate all of this variability. However, this is what real-life family physicians' patients are like.

2. Shorter time to peak serum free thyroxine index and "different absorption characteristics" for Synthroid are of no real consequence in a drug administered long-term with a half-life of 7 days.

3. The yet-unpublished, recently available data regarding serum thyrotropin (TSH) indeed show variability. This will not be surprising to clinicians monitoring patients taking levothyroxine. Further, it is not clear whether these are the same or different patients in each period, nor by what magnitude these TSH values fell out of range (Was it trivial or substantial?). There is also no data presented here to show that Synthroid is not just as variable as other products.

4. Drs Katz and Scherger refer to recent activities of the FDA, state legislatures, and state boards of pharmacy regarding "narrow therapeutic index" drugs, such as levothyroxine. These initiatives are not prompted by patients or providers concerned about quality. Rather, this agenda is being driven by the pharmaceutical industry through their research lobbying group, the Pharmaceutical Research Manufacturers Association (PhRMA). Interestingly, powerhouses such as Du Pont and Knoll find themselves in the ironic position of being an industry asking for more government rules and regulations.

The study by Dong et al provides head-to-head evidence for the bioequivalence of common forms of levothyroxine.[2] It is up to the dissenters to provide equally compelling evidence to the contrary. Clinical monitoring of levothyroxine therapy demonstrates that this is a variable drug, and we have no reason to believe that Synthroid is substantially different in this regard. Guidelines suggest annual TSH evaluation to monitor this variability.[3] And as Katz and Scherger suggest, it is prudent to measure TSH after switching from one formulation of levothyroxine to another, and doses may need to be adjusted to achieve optimal control. The price difference quoted by Katz and Scherger would lead to a yearly difference of $50 in drug cost. The cost of a TSH, approximately $45 at the University of Washington, would be recovered after just the first year of generic therapy (which ignores the cost of the TSH that would be checked annually anyway). If we switched even 4 million patients from their current Synthroid to generic, we would save $200 million per year after the first year. This is indeed an economic issue.

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FROM REAL QUIBBLES TO RESEARCH QUESTIONS

To the Editor:

Dr Stein's editorial comments[1] regarding our paper, "Gowning: Effects on Patient Satisfaction,"[2] are quite generous. We are deeply honored, though a bit reluctant, to accept the notion that our work constitutes "a paradigm shift." Perhaps, instead, our efforts may serve as a "recalibration" (as Dr Stein has also suggested) and return to such genuine paradigm-shifting thought as that first unveiled by George Engel, MD, 20 years ago this year.[3] In his biopsychosocial challenge to the biomedical model, Dr Engel threw down the gauntlet and became a champion to what today might be termed "patient-centered" care.

Dr Stein has raised some important curiosities, however, as to the contexts that bore out our research question. He writes, "I would have liked to have known the circumstances and timing in the authors' practice and working relationship in which questions about barriers, trust, satisfaction, time efficiency, and gowning were raised and heeded." In so asking, Dr Stein tempts us to tell our story. We do so both because we respect the questions he has posed (ie, what questions get asked and what questions get studied) and because we feel that the *Journal*'s readership may benefit from our experience.

The effects of gowning practices (either on patient satisfaction or clinic efficiency) might have taken the form of a wager or "gentleman's bet," if that were possible. It might have also disintegrated into a power struggle as to whose experience would prove to serve the "true reality"—that of a family medicine physician/clinic director or that of a clinical psychologist/behavioral science educator. Positions were well entrenched. The first author had never practiced or taught in a primary care residency where patients were routinely gowned before the physician arrived to hear the presenting problem—how dehumanizing, how "sterile." Certainly, such practices must detrimentally affect the doctor-patient relationship. The second author had never envisioned the routine practice of gowning as being anything other than practical, time efficient, and benign. Our third and fourth authors, in turn, contributed sociological and anthropological perspectives honed in the rigors of their extensive training.

A turning point in the evolution of these arguments came in the form of faculty development training. We had the privilege of hearing a simple message from Russell Schuh of the University of Pittsburgh. He encouraged our faculty to take what bothered us, to take what concerned us, to take what might actually aggravate us in our clinical/professional lives and transform these challenges into research questions. Such was the birth of our gowning question.

It is ironic that neither the first nor second author proved to be right (ie, gowning practices were not shown to have an impact on patients' trust in their doctors; they also did not significantly alter the length of the clinic visit). It is fitting that the big winners could, indeed, be our patients. We will continue to ask questions about what may affect our patients' satisfaction and clinical outcomes; we will settle our interdisciplinary struggles by means of the most cordial of venues—the honorable field of research. We challenge our colleagues to do the same.

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3. Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977;196:129-36.

CORRECTION

The final reference was missing from the editorial by Thomas L. Schwenk, MD, in the December issue (*Community-based teaching and academic medical centers: a fragile and uneasy alliance. J Fam Pract 1997; 45:482-4*). The reference is as follows: Vinson DC, Paden C. The effect of teaching medical students on private practitioners' workloads. Acad Med 1994; 69:237-8.