The vast majority of patients with hyperthyroidism do well only with levothyrixine alone. But there is a significant percentage of patients who do not do OK, and it really depends on the way we look at these patients. We can find the residual symptoms that can be attributed to hypothyroidism all the way up to 30, 40% of the population. It is debatable whether these symptoms are indeed secondary to hypothyroidism or due to confounders, comorbidities, patients perception. Again, most of the symptoms of hyperthyroidism are really are specific and it's incredibly difficult to sort out the symptoms, particularly in a disease condition which is chronic and its very slow progressing. So it's very difficult to define when the patient was doing OK.

All said, this situation is something that we need to deal with as a specialist and as a provider. And denying the reality that patients are not doing fine doesn't bring anywhere and actually can cause disaffection of patients and can prompt patients to look for very, shall we say, wild and unproven therapeutic approach which can result in real morbidity.

So the theoretical reason to consider a combination therapy, whereby we define combination therapy a mixture of T4 and T3, derives by the fact that the thyroid hormone production-- the thyroid hormone production from the thyroid gland is a mixture of T4 and T3. And so in patients who are devoid of endogenous production of thyroid hormone, the entire pool of thyroid hormone derives from exogenous synthetic T4 that then is metabolized in peripheral tissues in T3.

Again, that works well in most of the patients. But there are some measurable differences between endogenous production of thyroid hormone and exogenous thyroid replacement, particularly in patients with absolutely no endogenous thyroid hormone production, meaning patients who underwent thyroidectomy, for example. In these cases, there is pretty good evidence that, in order to achieve a normalization of TSH, the free T4 tends to be slightly higher and the T3 levels in circulation tend to be a bit lower compared to what would be a basal state, a normal state if you want to call it normal.

So this is some evidence that, yes, we are very good in normalizing TSH. In the aggregate, we're very good in making patients feeling OK, but we do not know whether this is exactly what we want to achieve in terms of a complete normalization of thyroid hormone and most important, whether we can ascribe some symptoms to the lack of the endogenous production of T3 or to the fact that we are administering thyroid hormone through the gastrointestinal system rather than direct secretion in the blood. And that's, obviously, something we do not know.

So to this end, there has been some intense studies in the experimental setting, experimental meaning in anima-- in experimental animals. And that goes back to 1990, 1994 when Dr. Morreale de Escobar clearly demonstrated that, in rats that are made hypothyroid, the restoration of serum level and tissue levels of thyroid hormone, meaning the ratio T4 and T3, could be achieved only by combination therapy whereby adding some T3 to the levothryoxine treatment.

And that has prompted a series of experiment, clinical experiments, to see whether this combination could relate to symptoms and signs of hyperthyroidism in patients. And the data are a bit all over the place. There is question from the perspective of the methodology employed in the studies, on the numerosity of patients in the studies, meaning the risk of not achieving enough statistical power. Multiple differences in study design, which make it very difficult to ascertain whether the lack of significant differences is due to lack of power or lack of effectiveness of multiple combination therapy.

But patients, often, are not doing well. And that, according-- it really depends on how that measure the-- again, it can be all the way up to 40% if we want to look for some, any symptoms ascribable to hypothyroidism. And patients are vocal and patients expected that we do something about. So at this point, we need to decide what do we do next? How do we go-- what are the boundaries of our therapeutic intervention? And most important, how can we prevent to cause iatrogenic morbidity?