

finavir. There was no evidence of genotypic or phenotypic resistance in HIV isolates from 51 subjects with viral rebound in the lopinavir–ritonavir group (69 percent); in contrast, among 96 subjects in the nelfinavir group (78 percent), resistance mutations (D30N, L90M, or both) were detected in 43 (45 percent).<sup>3</sup>

The study cited by Dr. Clotet<sup>4</sup> compared nelfinavir, zidovudine, and lamivudine with efavirenz, stavudine, and didanosine. The study by Robbins et al.<sup>5</sup> showed that the combination of nucleoside reverse-transcriptase inhibitors consisting of stavudine and didanosine is inferior to that consisting of zidovudine and lamivudine; therefore, it is problematic to cite these data to show that efavirenz and nelfinavir are equivalent in terms of virologic efficacy. Dr. Clotet's reanalysis of data from the study by Robbins et al. with the use of the primary end point of the study is not the most pertinent. If one uses the success of the first regimen in this type of analysis, then 210 of 310 subjects (68 percent) receiving efavirenz-containing regimens (groups 1 and 3) had successful treatment, as compared with 167 of 310 subjects (54 percent) receiving nelfinavir-containing regimens (groups 2 and 4). Even this type of analysis, with pooling of data across groups, may not be valid, since there are interactions for both

the primary and secondary end points, including failure of the first regimen, between at least two treatment factors: the initial combination of the two nucleoside reverse-transcriptase inhibitors and the initiation of treatment with efavirenz rather than with nelfinavir. These data suggest that strategies involving the use of ritonavir-boosted protease inhibitors or newer, more potent protease inhibitors may be important options for initial treatment in combination with other agents.

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## Prolactinomas

**TO THE EDITOR:** In the study protocol described by Colao et al. (Nov. 20 issue),<sup>1</sup> cabergoline was given at a dose of 0.5 mg per week to patients with nontumoral hyperprolactinemia, microprolactinomas, or macroprolactinomas and then stopped abruptly. I propose that cabergoline be tapered off rather than abruptly stopped, to avoid potential rebound hyperprolactinemia. The dose can be reduced from the typical dose of 0.25 mg twice a week, to 0.25 mg once a week, and then to 0.25 mg every other week before discontinuation. Serum prolactin levels can be measured one month after dose reduction and the reduction continued if the prolactin levels are normal. It is likely that cabergoline tapering, rather than withdrawal, will lessen the incidence of complications of hyperprolactinemia.

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**TO THE EDITOR:** Colao et al. indicate that many patients harboring prolactinomas who are treated with cabergoline remain in remission after drug withdrawal. Of the 36 percent of patients with macroprolactinomas in their study who had a recurrence of hyperprolactinemia after discontinuation of the drug (with a median time to recurrence of 18 months), none had recurrent tumor growth. The apparent discordance between the recurrence of hyperprolactinemia (indicating the potential for tumor growth) and the magnetic resonance imaging (MRI) findings suggests that follow-up was insufficient to determine the true rate of tumor control. Slow growth of prolactinomas has been recognized and

may be anticipated in some patients after the discontinuation of cabergoline; similarly, in some patients prolactin levels have been reported to rise after the discontinuation of bromocriptine.<sup>1</sup>

In an article in the same issue, Schlechte<sup>2</sup> provides an overview of the current approach to the management of prolactinoma. Although we agree that surgery for prolactinomas is recommended when medical therapy is ineffective, a surgical option for the treatment of microprolactinomas should be emphasized. A 91 percent cure rate over a follow-up period of at least five years was observed in a large series of patients with microprolactinomas.<sup>3</sup> Other surgeons have reported similar results,<sup>4,5</sup> indicating that resection is a reasonable option, especially in patients with microadenomas associated with prolactin levels of less than 200 ng per milliliter in whom surgical cure would be anticipated.<sup>6</sup>

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**TO THE EDITOR:** An omission in the discussion of prolactinoma by Schlechte is the problem presented by macroprolactin.<sup>1-4</sup> In the flowchart presented as Figure 2 of the article, an initial step in evaluating hyperprolactinemia should be the determination of whether increased measured levels of prolactin represent increased levels of active hor-

monone. Consultation with the laboratory may be of value.

Macroprolactin, a complex of prolactin and immunoglobulins, is not physiologically active.<sup>1-4</sup> However, macroprolactin has a longer half-life in the circulation than does free prolactin, resulting in increased total levels of circulating prolactin. Macroprolactinemia may account for up to 20 percent of all cases of hyperprolactinemia.<sup>1,2</sup> Identification of macroprolactinemia requires laboratory techniques that separate prolactin from macroprolactin before analysis,<sup>1-4</sup> although it may be suspected when different assay methods yield different results.<sup>4</sup>

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**DRS. COLAO AND LOMBARDI REPLY:** We thank Dr. Friedman and Dr. Couldwell and colleagues for their letters, which allow us to discuss a few important points related to the treatment of prolactinomas and the methods of cabergoline withdrawal. The issue of tapering cabergoline is very important. We withdrew cabergoline only from those patients whose prolactin levels remained normal during the reduction of the dose to 0.5 mg once a week or 0.25 mg twice a week. Whether a further dose reduction, to 0.25 mg once a week, would have improved the outcome of withdrawal should be the subject of further investigation. However, the nadir prolactin level during treatment correlated with persistent normoprolactinemia to a greater extent than did the dose of cabergoline. The patients in whom there was suppression of prolactin levels (to less than 5 µg per liter) during cabergoline therapy had the highest likelihood of maintaining normopro-

lactinemia after withdrawal. There was no difference in the outcome of withdrawal in patients with microprolactinomas and those with macroprolactinomas whose tumors disappeared on MRI studies.

Couldwell and colleagues suggest that surgery and its high rates of cure in the management of microprolactinomas (e.g., a 91 percent rate of cure over a follow-up period at least five years)<sup>1,2</sup> should not be forgotten, especially in patients with baseline prolactin levels of less than 200 µg per liter. We found higher base-line prolactin levels in patients with microprolactinomas who had a recurrence of hyperprolactinemia after withdrawal, and Amar et al.<sup>1</sup> observed a 100 percent rate of cure after five years in patients whose prolactin levels immediately after surgery were below 5 µg per liter. In this respect, the results of surgery and medical therapy of microprolactinomas share some features: the outcome is better in patients with lower base-line prolactin levels than in those with higher base-line levels.

The most relevant differences between surgery and medical therapy can be summarized as follows. Surgery should be performed in highly specialized centers, it is expensive, and it is not without complications,<sup>3</sup> even when new surgical techniques are used.<sup>4</sup> Medical therapy, in contrast, can be easily performed in any center where an endocrinologist is experienced in treating pituitary tumors. Medical therapy is inexpensive and can be successfully used for patients with microprolactinomas or macroprolactinomas. Although we agree that surgery can be offered to young patients with microprolactinomas, our study shows that lifelong treatment with cabergoline can be avoided by careful periodic treatment withdrawal, without clinical or neuroradiologic consequences.

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**DR. SCHLECHTE REPLIES:** The incidence of macroprolactinemia ranges from 18 to 42 percent when samples from reference laboratories are assayed, whereas the incidence is about 10 percent among patients in an endocrinology practice.<sup>1-3</sup> Most women with a preponderance of high-molecular-weight prolactin (i.e., those with macroprolactinemia) do not have the typical symptoms of hyperprolactinemia, but some have amenorrhea or galactorrhea, and the presence of macroprolactin does not totally rule out pituitary adenoma.<sup>3</sup> The ability to detect macroprolactin might help in the evaluation of idiopathic hyperprolactinemia and in some cases might eliminate the need for MRI studies of the pituitary. The difficulty is in the detection of macroprolactin.

Smith et al.<sup>4</sup> compared nine different assay systems commonly used in the United States and Europe and noted marked variability in the detection of prolactin in serum samples containing macroprolactin; Schneider et al.<sup>5</sup> also noted that prolactin assays vary substantially in their reactivity for macroprolactin. Although some are better than others, there is no single prolactin assay that will yield a normal level of monomeric prolactin in the presence of macroprolactin. Furthermore, there is no simple method of detecting macroprolactin, and many assays do not even describe techniques for its detection. Gel-filtration chromatography is expensive and is not used in clinical laboratories. Polyethylene glycol precipitation is simple and inexpensive but is not specific or quantitative, and serum pretreated with polyethylene glycol may not be compatible with all instrumented assays. Equipment manufacturers and clinical laboratories should clearly characterize assays with respect to macroprolactin and provide a procedure for its detection.

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## Effect of Incentive-Based Formularies on Drug Utilization and Spending

**TO THE EDITOR:** Huskamp et al. (Dec. 4 issue)<sup>1</sup> found that incentive-based formularies affect not only prescription-drug costs, but also patients' compliance with medications. Why do patients use less medication when offered more choice? One possible answer: incentive-based formularies create more complexity than choice.

Three-tiered pharmaceutical benefits are based on the assumption that physicians can serve as agents for their patients and prescribe the least expensive among similarly effective formulary options. But the average physician sees patients who, in total, are covered by more than 13 health plans,<sup>2</sup> each offering a unique formulary with individualized incentives. Unfortunately, physicians often inadvertently prescribe medications that require higher out-of-pocket costs for patients, with no marginal clinical benefit, because physicians are not aware of these costs, thus probably contributing to the observed decrease in patients' compliance.

This work calls for research to evaluate physicians' and patients' knowledge of and beliefs about incentives at the time of prescribing. We must also consider approaches to help physicians and their patients navigate complex formularies, especially since recent Medicare legislation endorses an increasing role for private health plans in the provision of prescription drugs.

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**TO THE EDITOR:** The study by Huskamp et al. demonstrates the need for thoughtful management of both financial incentives and their clinical and economic effects. Ever since the RAND Health Insurance Experiment, it has been known that greater consumer cost sharing can reduce both inappropriate and potentially beneficial care.<sup>1</sup> In an era of rising health care costs, the challenge is to reduce the former and maintain (or increase) the latter.

The copayment design of a pharmacy-benefit plan is important in engaging consumers, along with their physicians, in making choices about medications. Other components, however, are critical, including thoughtful tier placement of prescription drugs with use of an evidence-based process, consumer access to effective and easy-to-use decision-support tools, and seamless integration of pharmacy and clinical programs. In UnitedHealthcare's program, we continually assess emerging evidence to place medications in copayment tiers on the basis of total health care value, not just pharmaceutical spending. We also integrate our pharmacy programs with our other clinical initiatives to promote effective, evidence-based care, using data and evidence to assess overuse, underuse, and misuse of pharmaceuticals.

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