

comptroller general of the GAO, as long as dialysis facilities "receive a separate payment for each administration of each [separately billable] drug and the payment exceeds the costs of acquiring the drug, an incentive remains to use more of these drugs than necessary."

Under its monitoring policy, Medicare expects that providers, in addition to following the FDA label instructions for epoetin, will reduce the dose by 25% if the patient's hematocrit exceeds 39.0 (a hemoglobin level of 13.0 g per deciliter). Even if the dose is not reduced, CMS decreases the payment. This payment-reduction threshold recognizes clinical variability in maintaining hemoglobin levels in individual patients. Nonetheless, the House Committee on Ways and Means and others have criticized the CMS policy because the level that triggers a reduction in payment is higher than the FDA's maximum target level for patient care.

Medicare uses a bundled-payment approach to pay for most services. According to the GAO, extending this approach to all ESRD services would make treatment choices "payment neutral" and encourage "providers to operate efficiently, as they retain the difference if Medicare's payment exceeds the costs they in-

cur to provide the services."¹ For example, providers might administer epoetin to more patients subcutaneously, which requires considerably less drug than intravenous administration to achieve the same effect. Of course, the success of a global, prospectively set rate depends on the design of the implementation strategy. In addition to avoiding incentives for undertreating, critical issues include the reimbursement rate, how it is updated to reflect changes in costs and medical practice, and how Medicare adjusts payments to account for the distribution among centers of patients whose care is more or less expensive. Moreover, in the case of epoetin, other approaches to cost reduction could complement efforts to control utilization. Examples include a lower reimbursement rate, price competition with other medications, and legislation to provide Medicare with the authority to negotiate lower drug prices.

Under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress required CMS to submit, in October 2005, a report on how a bundled-payment system for ESRD would be designed and to start a 3-year bundling demonstration in January 2006.¹ In her testimony at the December hearings, Leslie

Norwalk, the acting CMS administrator, said that the agency generally supports shifting to such a system but wants to finalize the details first. The CMS report, however, has yet to be submitted, and the demonstration project has not started. Congress will have to decide whether to wait at least several more years for the results or to create a bundled-payment system before they become available.

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1. Report to the Chairman, Committee on Ways and Means, House of Representatives. End-stage renal disease: bundling of Medicare's payment for drugs with payment for all ESRD services would promote efficiency and clinical flexibility. Washington, DC: Government Accountability Office, November 2006. (GAO-07-77.) (Accessed December 12, 2006, at <http://www.gao.gov/cgi-bin/getrpt?GAO-07-77>.)
2. Steinbrook R. Haemoglobin concentrations in chronic kidney disease. *Lancet*. Published online November 17, 2006 (DOI: 10.1016/S0140-6736(06)69707-9).
3. USRDS 2006 annual data report: atlas of end-stage renal disease in the United States. Minneapolis: U.S. Renal Data System, 2006. (Accessed December 12, 2006 at <http://www.usrds.org/adr.htm>.)
4. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085-98.
5. FDA Public Health Advisory. Epoetin alfa (marketed as Procrit, Epogen); darbepoetin alfa (marketed as Aranesp). Rockville, MD: Food and Drug Administration, November 16, 2006. (Accessed December 12, 2006, at <http://www.fda.gov/cder/drug/advisory/RHE.htm>.)

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FOCUS ON RESEARCH

Drugs and Valvular Heart Disease

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In 1997, Connolly et al. reported that both racemic fenfluramine (Pondimin) and dexfenfluramine (Redux) were associated with val-

vular heart disease.¹ The valvular abnormalities seen in patients treated with these agents were distinctive. On echocardiography,

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leaflet thickening as well as chordal thickening and retraction were observed. Surgically removed valves were noted to have a glistening

white surface, with histologic evidence of a plaque-like process extending along the leaflet surfaces and encasing the chordae tendinae. These findings were similar to those in patients with heart-valve damage induced by serotonin-secreting carcinoid tumors.¹

This association of racemic fenfluramine and dexfenfluramine with valvular heart disease led to the withdrawal of both drugs from the market. Because of the observed similarity to carcinoid heart disease, and because fenfluramine and its active metabolite norfenfluramine are agonists at various serotonin (5-hydroxytryptamine, or 5-HT) receptors, Devereux urged caution "in the long-term use of other agents that act on serotonergic mechanisms."² Since a large number of commonly prescribed medications, including antidepressant, antipsychotic, anxiolytic, antimigraine, and other drugs, have serotonergic mechanisms, there was concern that numerous approved drugs might also cause valvular heart disease.²

In 2000, we and others reported that norfenfluramine is a potent agonist at 5-HT_{2B} receptors.³ These receptors are plentiful in human cardiac valves and appear to be essential for normal cardiac development. In contrast, norfenfluramine is devoid of appreciable activity at many other types of receptors that are plentiful in the heart, including all known biogenic amine (e.g., α_1 -, α_2 -, and β -adrenergic) receptors and peptide receptors.³ In subsequent studies, we found that ergotamine, an ergot derivative that has also been reported to induce valvular heart disease, activates 5-HT_{2B} receptors and that methylergonovine, the active metabolite of the prototypic valv-

ulopathic agent methysergide, is an extraordinarily potent 5-HT_{2B} agonist.⁴ Taken together, these findings implicated activation of 5-HT_{2B} receptors as a key step in initiating drug-induced valvular heart disease.

Valvulopathic drugs have been shown to induce mitogenesis in cultured interstitial cells from human cardiac valves by activating the 5-HT_{2B} receptor.⁴ My research group has suggested that valvulopathy induced by 5-HT_{2B} receptors is caused by the inappropriate mitogenic stimulation of normally quiescent valve cells, resulting in an overgrowth valvulopathy (see diagram).⁴ Although the precise signaling pathways leading to valvulopathy are unknown, 5-HT_{2B} receptors are known to activate mitogenic pathways through the phosphorylation of Src kinase and extracellular regulated kinases (ERK). Both classic G-protein-mediated signaling pathways and new pathways involving arrestin and other accessory proteins may be involved in activating the mitogenic pathways; it is also likely that cross talk with receptor tyrosine kinases is important for mitogenesis (see diagram).⁵

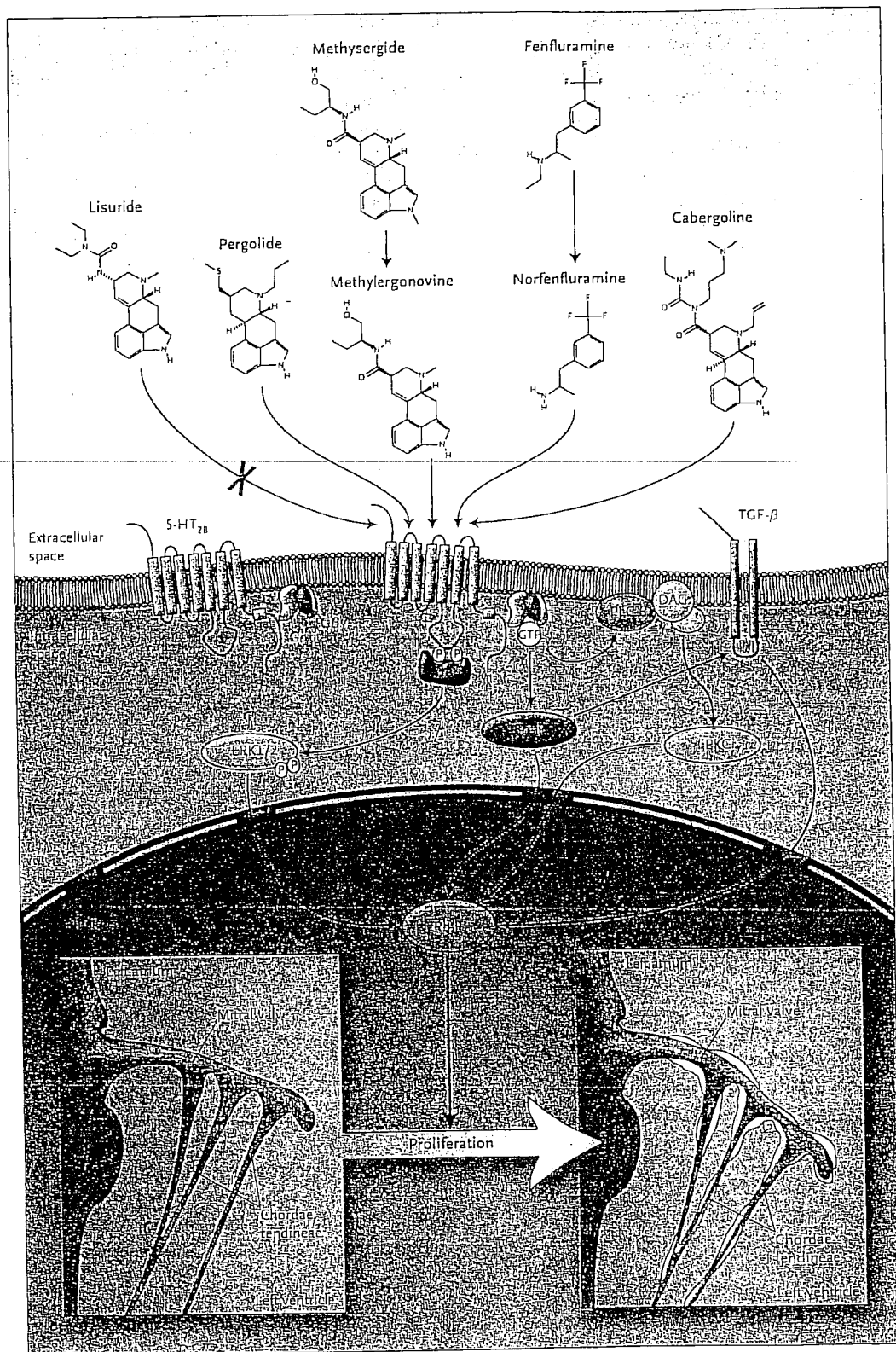
It was subsequently discovered that two antiparkinsonian dopamine agonists, pergolide and cabergoline, are potent 5-HT_{2B} agonists; they were therefore predicted to be valvulopathic agents.⁵ Other commonly prescribed antiparkinsonian drugs such as apomorphine, pramipexole, bromocriptine, lisuride, and roxindole are devoid of 5-HT_{2B}-agonist activity and, accordingly, were not expected to induce valvular regurgitation. As predicted, case reports of cabergoline- and pergolide-induced valvular heart disease soon appeared.

In this issue of the *Journal*, two

large European studies independently verify the association of valvular heart disease with pergolide and cabergoline. Schade et al. (pages 29–38) conducted a population-based study to investigate the associations between six dopamine agonists (bromocriptine, cabergoline, pergolide, lisuride, pramipexole, and ropinirole) and valvular heart disease. Only pergolide and cabergoline — the only two dopamine agonists that are also potent 5-HT_{2B} agonists — were significantly associated with cardiac-valve disease. Mitral, aortic, and tricuspid valves were affected. Lisuride, which is an agonist at two related serotonin receptors (5-HT_{2A} and 5-HT_{2C}) but is not a 5-HT_{2B} agonist, was not associated with valve disease. The findings concerning lisuride further implicate 5-HT_{2B} serotonin-receptor activation as a key step in the progression of drug-induced valvulopathy. Schade et al. also report that amantadine is associated with an increased risk of valvular heart disease. It will be important to determine whether amantadine (or one of its metabolites) also activates 5-HT_{2B} receptors.

In the second study, Zanettini et al. (pages 39–46) found that clinically significant regurgitation was discovered only in patients taking pergolide or cabergoline. The rates of drug-induced valvulopathy were high (23.4% and 28.6% in the pergolide and cabergoline groups, respectively, vs. 5.6% among controls) but were similar to those reported previously in a smaller study. In the Zanettini study, as in the study by Schade et al., drug-induced insufficiency was evident in mitral, aortic, and tricuspid valves.

These two studies reinforce the notion of a causal association be-



Molecular Mechanisms by Which 5-HT_{2B} Agonists Induce Valvular Heart Disease.

Both prescribed drugs (such as pergolide, cabergoline, and ergotamine) and their active metabolites (such as norfenfluramine and methylergonovine) activate 5-HT_{2B} receptors, a subtype of serotonin receptors. Chemically similar medications that do not activate 5-HT_{2B} receptors (e.g., lisuride) do not cause valvular heart disease, further implicating this receptor in the pathogenesis of heart-valve disease. Activation of 5-HT_{2B} receptors leads to the dissociation of the heterotrimeric G protein, liberating the Gαq subunit, which in turn activates phospholipase C-β (PLC-β). Activation of PLC-β leads to the activation of protein kinase C (PKC) through the mobilization of intracellular calcium and the liberation of diacylglycerol (DAG). Although all the specifics are not yet known, G proteins may also induce Src phosphorylation (forming Src-P) and activation, as well as the activation of the pathways of extracellular regulated kinases (ERK). In addition, Src-P may both mediate and enhance the activity of the transforming growth factor β (TGF-β) receptor, augmenting 5-HT_{2B}-stimulated mitogenesis. For many G-protein-coupled receptors, the binding of β-arrestin (βArr) may facilitate activation of ERK1 and ERK2. The final common pathway by which activation of 5-HT_{2B} receptors leads to mitogenesis probably involves the phosphorylation of retinoblastoma protein (Rb-P). Excessive cell division leads to an overgrowth valvulopathy and subsequent valvular dysfunction.

tween 5-HT_{2B} agonism and valvular heart disease. Such an association has now been seen with drugs for diverse indications, including anorectic agents (fenfluramine), antimigraine drugs (dihydroergotamine, methysergide, and ergotamine), and antiparkinsonian agents (pergolide and cabergoline). On the basis of these findings, my colleagues and I have urged pharmaceutical companies and regulatory agencies to screen candidate drugs and their major metabolites at 5-HT_{2B} receptors comprehensively before launching clinical trials, in order to prevent "fen-phen"-type disasters.^{3,5} Clearly, practitioners should avoid prescribing drugs that are potent 5-HT_{2B}-receptor agonists — a growing list of medications that now includes ergot derivatives (ergotamine, methysergide, and dihydroergotamine), dopamine agonists (pergolide and cabergoline), and amphetamine derivatives (fenfluramine and methylenedioxy-

methamphetamine [MDMA, or "ecstasy"]).

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1. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997;337:581-8. [Erratum, *N Engl J Med* 1997;337:1783.]
2. Devereux RB. Appetite suppressants and valvular heart disease. *N Engl J Med* 1998;339:765-6.
3. Rothman RB, Baumann MH, Savage JE, et al. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* 2000;102:2836-41.
4. Setola V, Hufeisen SJ, Grande-Allen KJ, et al. 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. *Mol Pharmacol* 2003;63:1223-9.
5. Setola V, Roth BL. Screening the receptorome reveals molecular targets responsible for drug-induced side effects: focus on 'fen-phen.' *Expert Opin Drug Metab Toxicol* 2005;1:377-87.

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