

solutions than smaller sums on maintaining protected time for their staff to drive change. And yet clinicians know more than outsiders about health care's customers and context; they have street credibility and established trust relationships in an environment where those characteristics count; they can often reuse experiences in multiple projects; and they're usually mission-driven to improve outcomes. They also don't then resell the lessons learned; they give them away, in presentations and papers.

These insiders, however, often face three barriers to innovation. First, principles of rapid-cycle innovation are part of neither medical training nor clinicians' experience. Even in academic medical centers emphasizing research, clinicians who conduct controlled experiments in the laboratory often don't consider deploying them when seeking to improve care delivery. But just as operating-room "timeouts" introduced new discipline in clinical settings, we've seen care teams embrace rapid validation methods, testing and evaluating new ideas quickly.

Second, insiders' experience

can become constraining. Henry Ford is often credited with saying that had he asked his customers what they wanted, they would have said "faster horses." Though he apparently never said that, the story highlights the trap of envisioning incremental gain along established dimensions and the difficulty of envisioning the kind of change that replaces horses with cars. It's important to enforce divergent thinking, in part by using analogies when breakthroughs from outside health care can expand our vision.

Third, clinicians are busy. Health care organizations, operating on thin margins, rarely allow for slack in staff work. Many organizations say they simply cannot introduce time for stepping back and reimagining that work: it's too costly to take the workers who add the most value off the front lines. But it can be done with selected individuals and at strategic times. Companies that have begun insourcing innovation couldn't imagine doing so before they'd designed new time-allocation practices. Time for engagement is even more critical in health care: new ideas

create no value until they're implemented, and effective implementation in health care requires clinician acceptance.

Forward-thinking health systems understand the obligation to improve value. Health care can benefit from outside perspectives in this endeavor, but clinicians have the requisite drive, experience, and context to be productive innovators. If we adapt and internalize proven innovation principles from other fields, much effective innovation can come from within.

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## FDA Approval of Paroxetine for Menopausal Hot Flashes

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The recent approval by the Food and Drug Administration (FDA) of paroxetine (Brisdelle, Noven) for the treatment of moderate-to-severe vasomotor symptoms associated with menopause was distinctive for at least

two reasons. First, it offered the first nonhormonal option to women who cannot or do not want to use hormonal medications to treat their menopausal vasomotor symptoms. Second, the approval ran counter to the rec-

ommendation of the FDA Reproductive Health Drugs Advisory Committee, which had concluded, by a vote of 10 to 4, that the overall benefit-risk profile of Brisdelle did not support approval. The FDA always carefully

considers the advice from its advisory committees but is not required to follow the committee recommendations. Why did the FDA decide, despite a negative vote from an advisory committee, to approve Brisdelle?

Vasomotor symptoms, also known as hot flushes or hot flashes, occur in as many as 75% of menopausal women in the United States. Vasomotor symptoms are not life-threatening but can greatly affect quality of life for many women, may transiently disrupt daily activities, and can impair sleep. For decades, hormonal therapy had been the only FDA-approved treatment for menopausal vasomotor symptoms, with estrogen monotherapy recommended for women who have had a hysterectomy and estrogen-progestin combination therapy prescribed for women who have not. Hormonal therapy is highly effective for treating vasomotor symptoms, but health risks in some women became apparent about a decade ago, with the release of reports from the Women's Health Initiative.<sup>1,2</sup> The reports concluded, on the basis of a large randomized, controlled trial, that some risks, such as invasive breast cancer, coronary artery disease, stroke, and venous thromboembolism, were increased with the combined use of conjugated equine estrogens and progestin, whereas the risk of stroke and the risk of deep vein thrombosis were increased with the use of conjugated equine estrogens alone. Owing to these reports, many women either have chosen not to use hormonal therapy to treat their symptoms or have not been offered such therapy because of coexisting conditions. Overall, use of hormonal thera-

py has decreased considerably in the past decade — a trend that underscores an unmet need for a nonhormonal treatment option for vasomotor symptoms.

Brisdelle contains 7.5 mg of paroxetine, a selective serotonin-reuptake inhibitor, and is taken at bedtime. Paroxetine is the active moiety in Paxil (paroxetine hydrochloride, GlaxoSmithKline) and Pexeva (paroxetine mesylate, Noven), which are approved for the treatment of several psychiatric conditions, including major depressive disorder. Both Paxil and Pexeva are typically taken in the morning, with doses starting at 10 to 20 mg and increased gradually, as needed, to a maximum recommended dose of 40 to 60 mg, depending on the condition being treated.

The efficacy of Brisdelle was established in two randomized, double-blind, placebo-controlled, multicenter clinical trials. Among a total of 1184 menopausal women who had a median of 10 moderate-to-severe hot flushes per day, Brisdelle was shown to provide modest relief in comparison to placebo. For example, at week 12 in one study, there was a median reduction from baseline of 5.9 moderate-to-severe hot flushes per day with Brisdelle as compared with a median reduction of 5.0 per day with placebo (median treatment difference, 0.9;  $P < 0.01$ ). At week 12 in the second study, there was a median reduction from baseline of 5.6 moderate-to-severe hot flushes per day with Brisdelle as compared with a median reduction of 3.9 per day with placebo (median treatment difference, 1.7;  $P < 0.001$ ). Despite this modest effect, more women who used Brisdelle than women who used placebo considered the

reduction in frequency of their hot flushes to be clinically meaningful. In addition, Brisdelle remained efficacious at 6 months, the latest time point assessed. This is an important finding, because a lack of efficacy at 6 months after treatment initiation would call into question its usefulness for this fairly chronic condition.

The safety profile of paroxetine, when used at higher doses to treat psychiatric disease, is well-established. Like all antidepressant medications, the labels for Pexeva and Paxil have a boxed warning describing the risk of suicidality in children and young adults. In addition, paroxetine-containing products are contraindicated in patients who have known hypersensitivity to the product ingredients, those with recent or current use of monoamine oxidase inhibitors, and those using thioridazine or pimozide. Other drug-drug interactions can also pose safety concerns, as can the association of paroxetine with other risks, such as bleeding events, hyponatremia, and akathisia.

Because the availability of a nonhormonal treatment for vasomotor symptoms may be especially important to women who are undergoing treatment for breast cancer or who are at risk for developing breast cancer, the potential for a drug-drug interaction between tamoxifen and Brisdelle deserves special consideration. Paroxetine is a strong inhibitor of the cytochrome P-450 CYP2D6 enzyme, which converts tamoxifen into endoxifen, a metabolite that contributes substantially to the pharmacologic activity of tamoxifen. The coadministration of paroxetine (10 mg per day for 4 weeks) in women who use

tamoxifen can decrease plasma concentrations of endoxifen by 64%.<sup>3</sup> The effect of paroxetine on tamoxifen efficacy, as measured by the risk of breast cancer relapse and death, remains unclear.<sup>4,5</sup> The Brisdelle label warns prescribers to weigh the likely benefit of Brisdelle for treating vasomotor symptoms against the risk of possible reduced effectiveness of tamoxifen.

Brisdelle's modest efficacy and concerns about suicidal ideation certainly influenced the advisory committee's 10-to-4 vote against approval. But recognizing that no hormone-free drug product had been approved to treat vasomotor symptoms, and after careful review of the efficacy results, the FDA concluded that Brisdelle offers a clinically meaningful benefit for some menopausal women. In addition, the Brisdelle clinical trials did not identify any new safety concerns regarding paroxetine. In fact, Brisdelle did not differ much from placebo with respect to reported adverse reactions. In contrast to higher doses

of paroxetine-containing products, Brisdelle doses do not have to be tapered before use is discontinued.

Furthermore, many of the known safety concerns regarding paroxetine, such as drug-drug interactions, can be anticipated and often avoided with appropriate patient selection. Although the risk of suicidality associated with Brisdelle is uncertain, it is noteworthy that the concerns about suicidality associated with higher doses of paroxetine pertain to children and young adults, a population for whom Brisdelle clearly is not indicated. Nonetheless, the Brisdelle label recommends monitoring patients for suicidal thoughts and behaviors and discontinuing treatment if there is worsening depression or suicidality. Patients are also informed of these risks through a medication guide, which, by law, must be provided every time the medication is dispensed.

On the basis of all the above considerations, the FDA considers Brisdelle to be a useful and reasonably safe nonhormonal op-

tion for treating moderate-to-severe vasomotor symptoms in menopausal women.

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