A look at delayed- vs. extended-release Rxs

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Pharmaceutical manufacturers often create new dosage formulations of the same active ingredient. Are you aware of the implications of these sometimes subtle differences? How many times have you used the terms *delayed-release* and *extended-release* interchangeably? Many Food & Drug Administration-approved drugs are available in multiple product formulations—immediate-release, delayed-release, and extended-release. Although they contain the same active ingredient and are available in identical strengths, they are not bioequivalent. So it is important for practitioners to recognize these differences to ensure the correct product formulation and dose are dispensed.

Depakote (divalproex sodium) is an example of such product-line extension. It is available as delayed-release capsules (Depakote Sprinkles), enteric-coated delayed-release tablets (Depakote), and enteric-coated extended-release tablets (Depakote ER). Several medication error reports have been received over the past several years which indicate a lack of understanding of the product differences between the different formulations of Depakote.

Product(s)/strength	Formulation	FDA approval date
Depakote 250 mg, 500 mg	Enteric-coated delayed-release	1983
Depakote 125 mg	Enteric-coated delayed-release	1984
Depakote 125 mg	Sprinkle delayed-release	1989
Depakote ER 250 mg, 500 mg	Enteric-coated extended-release	2002

In 2004, FDA received two medication error reports about institutions making formulary decisions based solely on frequency of dosing without considering the inherent pharmacokinetic differences between the delayed-release and extended-release formulations. Another report, in 2005, documented hospital personnel crushing Depakote tablets prior to giving them to a patient. A 2006 medication error report documented the reporter, a pharmacist, using *delayed-release* and *extended-release* interchangeably. Also in 2006, FDA received a medication error report that documented a hospital pharmacy defining Depakote delayed-release tablets as the "twice-a-day" formulation, and Depakote ER as the "once-a-day" formulation. Thus, when a patient was admitted taking Depakote ER 750 mg twice a day for seizure control, the pharmacy incorrectly dispensed Depakote delayed-release tablets.

The United States Pharmacopeia (USP) defines *delayed-release tablets* as enteric-coated to delay release of the medication until the tablet has passed through the stomach to prevent the drug from being destroyed or inactivated by gastric juices or where it may irritate the gastric mucosa. USP defines *extended-release* tablets "formulated in such a manner to make the contained medicament available over an extended period of time following ingestion." Both the delayed-release and extended-release formulations of Depakote are enteric-coated but not interchangeable.

Pharmacokinetic studies have shown that when Depakote ER is given in equal total daily doses, its bioavailability is approximately 10% less than that of the delayed-release tablets. Thus, an equivalent dose of either dosage form does not provide an equivalent pharmacokinetic profile. Product confusion may therefore result in significant clinical effects in patients.

Asked what contributed to the product confusion, almost all reporters said they never knew there was a difference between delayed-release and extended-release dosage formulations and did not know of the introduction of the new extended-release formulation. Other contributing factors included the sound-alike names Depakote ER (extended-release) and Depakote DR (delayed-release), visual similarities in the unit-dose packaging, and computer entry errors due to the overlapping portion of established names (divalproex sodium), and overlapping product strengths (250 mg and 500 mg).

It is important for practitioners to understand the pharmacokinetic differences for each formulation of Depakote, and to implement strategies to minimize the potential unwanted outcomes and errors. Strategies might include clearly marking the shelves where Depakote delayed-release and Depakote extended-release products are stored, to make them more distinguishable—especially since they are stored adjacent to each other. Also consider highlighting or flagging the different Depakote products in computer menus so that each formulation has a different appearance to decrease computer selection errors. Finally, educate the pharmacy staff on the product differences so that knowledge deficits will not contribute to Depakote errors in the future.

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