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New Uses for Older Drugs: The Tales of Aspirin, Thalidomide, and Gabapentin

In this issue of *Mayo Clinic Proceedings*, 2 articles describe original research in which gabapentin therapy produced novel, beneficial effects in patients with chronic neurologic conditions. Bogan et al[1] report that gabapentin enacarbil, a gabapentin prodrug, may be useful for maintenance treatment of restless legs syndrome. Pistoia et al[2] document a case series that suggests efficacy of gabapentin for treating opsoclonus-myoclonus syndrome in paralyzed patients with locked-in syndrome. The benefit from gabapentin treatment included opening a window of communication with the otherwise noncommunicative patients. These descriptions of novel uses for established drugs represent a growing trend in medicine: (1) gabapentin (developed as an antiseizure medication) currently being used to treat chronic pain conditions and the aforementioned conditions; (2) thalidomide (developed as a sedative and once removed from the market because of its propensity to produce birth defects) and its congeners currently being used to treat neoplastic diseases; and (3) aspirin, introduced as an analgesic, currently being used to treat a host of ills. As a corollary, when the modern pharmacopoeia is viewed in aggregate, the number of off-label uses of medicines is growing at an impressive rate. The prototype drug for such expansion of uses is aspirin; however, newly introduced drugs are accomplishing in years and decades what aspirin took millennia to achieve.

To understand off-label uses of medications, consider the trajectory of aspirin from botanical curiosity to iconic global brand as related by the Bayer Health Care corporation Web site.[3] In 400 BC, the Greek physician Hippocrates described the use of the bark and leaves of the willow tree (rich in a substance called *salicin)* to relieve pain and fever.[3] In 1832, a French chemist, Charles Frédéric Gerhardt, experimented with salicin and created salicylic acid.[4] In 1897, the chemist Felix Hoffmann at Bayer in Germany chemically synthesized a stable form of aspirin powder that relieved his father's rheumatism.[3] In 1899, Bayer distributed aspirin powder to physicians to give to their patients, and it became the number one drug worldwide.[3] Aspirin was taken to the moon by the Apollo astronauts in 1969, yet its principal mechanism of action was not discovered until the 1970s.[5] In 1988, aspirin's role expanded beyond that of pain reliever to that of potential lifesaver when the US Food and Drug Administration (FDA) proposed using aspirin to reduce the risk of recurrent myocardial infarction and to prevent recurrent transient ischemic attacks or ministrokes in men.[6,7]

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In 1988, the aspirin component of the Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of 22,000 apparently healthy men, was terminated early because of the extreme reduction in the risk of a first myocardial infarction.[3] In 1996, when the Massachusetts Institute of Technology performed a survey in which they asked respondents to identify an invention they could not live without, twice as many people chose aspirin as the personal computer.[3] Recently, Bayer Health Care filed a citizen petition with the FDA to broaden the professional labeling of aspirin to include indications for the prevention of a first myocardial infarction in individuals at moderate or greater risk of coronary heart disease.[3] Investigators have also explored the use of aspirin in the prevention of colon cancer, esophageal cancer, and other diseases. Thus, from antiquity to modern times, aspirin has proven to be one of the most consequential, indispensable pharmaceutical marvels ever created. Remarkably, its current uses are far beyond those envisioned by the original creators of the drug.

Address correspondence to Joseph I. Sirven, MD, Department of Neurology, Mayo Clinic in Arizona, 5777 Mayo Blvd, Phoenix, AZ 85054 (sirven.joseph@mayo.edu).

Now consider thalidomide. The compound was first synthesized in 1953 by Ciba, a Swiss pharmaceutical firm.[8] The drug was introduced into the world market by Chemie Grünenthal as a nonaddictive, relatively "risk-free" sedative (compared to the more commonly used barbiturates). The drug gained market share and was likely to enter the US market. However, by 1961 the drug was taken off the world market, and the request for US marketing was withdrawn because of thalidomide's potent teratogenicity, which could manifest after ingestion of a single pill. The thalidomide experience led to a fundamental restructuring of the FDA's role and responsibility in future drug approvals.[9]

A few decades later, the teratogenic effect of thalidomide was exploited for its antineoplastic properties. Several major trials led to approval of thalidomide for the treatment of multiple myeloma and several related plasma cell disorders.[8] Thalidomide and potential analogues are being evaluated for potential treatment of various conditions, including myelofibrosis, Kaposi sarcoma, and renal cell carcinoma. Nonneoplastic indications are also being explored for inflammatory conditions, with careful monitoring of potential adverse effects. The thalidomide story is a fascinating reminder that new uses can be found for drugs, even after they have been left for dead.

This brings us to gabapentin. This drug was purposefully synthesized to mimic the chemical structures of the neurotransmitter γ-aminobutyric acid by Satzinger, coincidentally for another German company, Gödecke AG.[3] Gabapentin was approved by the US FDA in 1994 for use as an adjunctive medication to control partial seizures; it was effective when used in combination with other antiseizure drugs.[10] In 2002, an indication was added for the treatment of postherpetic neuralgia (neuropathic pain after shingles), other painful neuropathies, and nerve-related pain. Although its mechanism of action is not completely delineated, gabapentin is thought to exert its clinical effect by selective binding of the α2δ subunit of voltage-dependent calcium channels.[11] Gabapentin is one of two medications used in the PROMETA treatment protocol for methamphetamine, cocaine, and alcohol addiction.[12] Gabapentin, at a dosage of 1200 mg at bedtime for 40 to 60 days, is reported to have some potential for reducing the cravings and withdrawal symptoms associated with discontinuation of methamphetamine use.[12] It also helps those addicted to prescribed pain medications and reduces withdrawal syndromes.[12]

More recently, gabapentin has gained favor for treating a myriad of neurologic conditions. Ironically, despite the fact that the drug was invented and synthesized for its use in seizure prevention, its smallest market today is epilepsy and seizures. A number of off-label or unapproved uses of gabapentin have been reported, including treatment of bipolar disease, neuropathic pain, diabetic neuropathy, complex regional pain syndrome, attention deficit disorder, restless legs syndrome, trigeminal neuralgia, periodic limb movement disorders of sleep, premenstrual syndrome, migraine headache, and drug and alcohol withdrawal seizures.[13,14] All these putative uses have led to multibillion dollar drug sales.

With blockbuster status confirmed, a dark side of the story emerges. In 2003, a federal jury evaluated whether Pfizer Incorporated violated antiracketeering laws in promoting its epilepsy drug gabapentin (Neurontin) for unapproved uses. The case stemmed from a claim from the Kaiser Foundation Health Plan that it was misled into believing gabapentin was effective for off-label treatment of migraines, bipolar disorder, and other conditions. Pfizer countered that Kaiser physicians still recommended gabapentin for those uses even after Kaiser sued Pfizer. A court ruling went against Pfizer.[15] In September 2009, Pfizer finalized the settlement with the US Department of Justice for a record-shattering $2.3 billion.[16]

In this month's issue of *Mayo Clinic Proceedings*, 2 reports further expand the potential indications of gabapentin for 2 dramatically different conditions with 2 very different approaches to evaluating efficacy. Bogan et al[1] investigated the long-term maintenance treatment of restless legs syndrome with oral gabapentin enacarbil via a randomized, controlled study. The primary objective of the research was to assess the maintenance of efficacy and tolerability of gabapentin enacarbil, a gabapentin prodrug, in patients with moderate to severe primary restless legs syndrome. This study (conducted from April 2006-November 2007) consisted of a 24-week single-blind treatment phase, and a 12-week randomized double-blind phase that applied only to responders from the initial portion of the research. The primary end points were (1) the proportion of patients whose restless legs symptoms relapsed (as judged by clinical instruments at least 1 week later) and (2) withdrawal from drug treatment because of lack of efficacy or adverse effects during the double-blind phase. The single-blind phase was completed by 221 patients, and the double-blind phase by 168 patients. A smaller proportion of the gabapentin-treated patients (9%) experienced relapse compared with the placebo-treated patients (23%; P=.02). The most common adverse effects of treatment were somnolence and dizziness. The authors suggest that the findings show a positive result for the use of gabapentin enacarbil for the management of restless legs syndrome.

Pistoia et al[2] reported on the use of 1200 mg of gabapentin via percutaneous endogastric tube for the management of opsoclonus-myoclonus syndrome (also known as

dancing eye syndrome) in 4 patients with the locked-in syndrome. Opsoclonus-myoclonus syndrome is characterized by combined horizontal, vertical, and/or torsional dysconjugate saccadic oscillations and spontaneous and continuous eye oscillations in a variety of directions beyond patients' control. Patients with the locked-in syndrome have only one means of communicating and that is by using eye movements; thus, the opsoclonus-myoclonus syndrome is a primary barrier to communication. Gabapentin therapy resulted in a rapid and long-lasting resolution of the opsoclonus-myoclonus symptoms without adverse effects. After 2 weeks, patients had voluntary attempts to communicate through eye blinking and thereafter regained full, voluntary control of eye movement, enabling them to communicate by using eye-controlled brain-computer interfaces. The authors concluded that gabapentin use in patients with the locked-in syndrome who have opsoclonus-myoclonus syndrome can result in a dramatic improvement in quality of life because it restores a vital communication channel.

These 2 studies demonstrate very different methods for establishing the clinical management of 2 unrelated conditions. Because gabapentin has been used for so many indications, concerns remain that pharmaceutical companies are simply trying to find new potential revenue markets for their older drugs. Although the agent being tested in the study by Bogan et al is a gabapentin prodrug, mechanistically its effect is exerted by gabapentin. Discovering agents that relieve restless legs symptoms can improve a patient's life. However, it is unclear whether a 9% relapse rate compared with the placebo's 23% relapse rate truly translates into an important clinical finding. The clinical end points measured may be appropriate for the controlled world of clinical trials, but is this meaningful for physicians in practice? The answer to that, of course, is unknown.

Are clinical trials applicable to real-world experience? Complex randomized, placebo-controlled multicentered trials such as that reported by Bogan et al often may have limited generalizability. Patients included in randomized controlled trials, doses of medications used, outcomes measured, and the effect of an intervention are not always the most appropriate for, or the most reflective of, common clinical practice. Placebo studies may have minimal applicability to practice if the patients are somewhat atypical. The interventions provided may be unique; the outcome measures may not be clinically meaningful. Furthermore, if an immense number of participants are entered into the trial, the results may become statistically significant even when differences among treatments are so small as to be clinically unimportant. Because of these many confounding factors, practicing physicians may have difficulty sorting out whether a given agent may be truly helpful or beneficial for the purposes for which it is intended. Moreover, a formulary committee may decide that, regardless of a trial or FDA indication, a particular drug is not sufficiently cost-effective for purchase and stocking. This creates confusion for physicians.

In contrast, the small case series by Pistoia et al has a potential profound impact for the treatment of such patients. Given that gabapentin has few serious adverse effects and the potential benefit to patients with the locked-in syndrome and opsoclonus-myoclonus syndrome is so momentous, the benefits of using gabapentin for this situation vastly outweigh any potential risks from the drug. Moreover, opsoclonus-myoclonus syndrome in patients with the locked-in syndrome is so relatively uncommon that a double-blind study is not feasible; thus, small observational studies serve as the main source of clinical evidence. However, this means that a small study could turn out to be the cornerstone for clinical practice with no other evidence.

This all brings us back to where we started. Is gabapentin the new wonder drug of the millennium? Will journals such as the *Proceedings* be discussing the various new off-label indications of gabapentin a century down the road? In 2001, an analysis of the US IMS Health and National Disease and Therapeutic Index found that 21% of all written prescriptions were for off-label uses. Of specific medications, gabapentin had the greatest proportion of off-label uses at 83%.[17] Given the cost constraints of trying to obtain an FDA-approved indication, how do we reconcile off-label uses of medications in an ethical and transparent manner? Will gabapentin be like aspirin, a must-have agent that all humans will need to take to function on a daily basis? The answers, of course, are unknown, but in light of the economy of scale at stake, we can be certain that gabapentin and off-label uses will dominate discussions for years to come. The tales of aspirin, thalidomide, and gabapentin are humbling reminders that the future uses of any given therapeutic agent are impossible to predict.

Joseph I. Sirven, MD
Department of Neurology
Mayo Clinic in Arizona
Phoenix

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