OPINION

A Patient-Centric Model for Discontinuation of a Single-Sourced Approved Drug

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When and how to discontinue an obsolete single-sourced approved drug? Transitioning patients to newer therapies in diseases such as epilepsy where therapeutic responses are often idiosyncratic presents a significant clinical challenge. Compassionate use programs for older approved drugs require rigorous oversight, especially when patient numbers are small. The discontinuation of a compassionate use program for trimethadione, a 70-year-old antiepileptic drug, highlights the issues and approaches needed to adequately focus on patient interests and needs.

A relatively underexamined issue for approved but clinically obsolete pharmaceutical products is how and when to discontinue them while respecting patient interests and needs. A little-used antiepileptic drug, trimethadione (3,5,5-trimeth yloxozolidine-2,4-dione), raised this issue for its manufacturer. Abbott Laboratories was the manufacturer of trimethadione until 2013 when Abbott's Pharmaceutical Products Division became a separate company, AbbVie Inc. Working with consulting ethicists, a drug discontinuation strategy was created, which may serve as a useful model for the retirement of other single sourced obsolete drugs.

Trimethadione represents one of several oxazolidine-2-4-dione drugs that have well-established antiseizure properties.[1,2] The antiseizure activity of trimethadione was first discovered based on its activity to reduce pentylenetetrzol-elicited seizure thresholds in rodents.[3] Subsequently it was shown that trimethadione selectively reduced "petit mal" or absence seizures in epilepsy patients.[4]

Trimethadione (Tridione) was approved in the United States in 1946 for the control of "petit mal" (absence) seizures refractory to treatment with other drugs. Following approval, trimethadione experienced rapid adoption in clinical practice due primarily to its efficacy for managing absence seizures and the comparative lack of alternative therapies for this seizure type at that time.[2] However, trimethadione therapy is associated with many potentially serious side effects, including rash, blood dyscrasias, renal and ocular dysfunction, lupus and myasthenia-like syndromes, and teratogenicity.[2,5] Additionally, the approved synthetic process for the manufacturing of trimethadione is complex and involves some special environmentally challenging controls.

Since the approval of trimethadione, more than two dozen antiepileptic drugs have entered clinical practice, many of which are differentiated from trimethadione in terms of improved benefit/risk profiles for the management of specific seizure disorders.[6] As a result, the clinical utilization of trimethadione decreased significantly during the 1980s and 1990s in favor of these newer agents.[7] In 1995 Abbott Laboratories, the sole manufacturer of trimethadione, discontinued marketing of the drug due to its limited use (~150 patients) and changes in medical practice.[7,8]

In response to requests from patients and their advocates including healthcare providers (HCPs), Abbott Laboratories, in consultation with the US Food and Drug Administration, initiated a compassionate use program to allow the remaining trimethadione-receiving patients continued access to the drug at no cost to them. This decision was based on the fact that these patients' seizures were well managed, and the perceptions of patients at that time and their healthcare providers that trimethadione was the only effective antiepileptic drug for them. Continued access to trimethadione under this compassionate use program required voluntary patient enrollment, which was approved through the manufacturer's medical services/medical information function.

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Following written request by each patient, their healthcare provider was contacted directly by the manufacturer to obtain Health Insurance Portability and Accountability Act authorization, patient demographic information, and the patient's dosing requirements. Prescription refills were provided based only on trimethadione prescriber request, and drug product was shipped from the manufacturer directly to the healthcare provider. Each healthcare provider was responsible for compliance with individual state drug-dispensing laws.

Over the course of the next two decades, the number of patients receiving trimethadione remained small, decreasing to approximately 50–60 patients as of 2015. Periodic patient surveys during this timeframe indicated that the humanitarian access program participants varied widely in age (~15–88 years), had generally good seizure control across a spectrum of seizure types, and experienced few if any of the tolerability issues associated with trimethadione use. Many of these patients received more than one medication to manage their seizures. Since these patients experienced generally good seizure control over many years, the majority were under the care of physicians who were not specialists in neurology or epilepsy.

In 2016, due to impending changes at the only approved manufacturing site and in the synthetic process for producing trimethadione, and also in the time required to satisfy associated regulatory validation requirements, a continuous supply of trimethadione was no longer available. However, the last available lot of trimethadione was sufficient to enable the manufacturer to develop a structured process that would make it possible for the remaining trimethadione patients to gradually transition to other appropriate therapies.

STRATEGIC OBJECTIVES

In order to avoid any undue hardship for patients transitioning to other appropriate therapies, a structured process was developed to:

1. Broadly communicate the transition plan to discontinue the trimethadione compassionate use program well in advance of expiry of the last remaining drug lot
2. Provide specific instructions to current prescribers and patients regarding timelines
3. Provide resources to facilitate HCP efforts to transition their patients from trimethadione to other appropriate therapies with minimal impact on the patient's treatment plan
4. In parallel, to ensure the efficient discontinuation of the trimethadione compassionate use program without creating a supply shortage for patients still on the drug

THE PROCESS

In order to fulfill these strategic objectives, the manufacturer consulted with external bioethical and medical experts to develop a patient-centric, fair plan to close the trimethadione compassionate use program. The recommended transition program contained three major components. First, the available supply of trimethadione was managed by the manufacturer to provide sufficient time for these patients and their healthcare providers to develop an orderly and individualized transition to appropriate alternative therapies. Second, since many of the remaining trimethadione prescribers were not epilepsy specialists, the manufacturer provided these HCPs with access to an independent epileptologist who had specific expertise in antiepileptic drug transitions. This consultation resource was provided to trimethadione prescribers only, did not involve direct patient interactions, and no patient-related or specific treatment plan information was shared with the manufacturer. Third, a uniform communication plan was developed to continually and transparently update trimethadione patients and prescribers of the changes in trimethadione availability. These communications included multiple telephone contacts with trimethadione prescribers as well as periodic letters directed to both HCPs and patients. Trimethadione prescribers were also routinely reminded of the available access to an independent epilepsy specialist to help them develop therapy transition plans as needed. An additional component of the communication plan involved informing relevant patient advocacy groups and medical societies of the changes in trimethadione availability to ensure all stakeholders had up-to-date, comprehensible information regarding the drug supply, transition plan, and patient support mechanisms.

The trimethadione transition program was initiated mid-2017. The initial communications to the trimethadione prescribers and their patients indicated that there was sufficient trimethadione available for a 12-month transition to other appropriate therapies, and an explanation of why the drug would no longer be available through the compassionate use program. This year-long period compares favorably with state and federal regulations requiring Medicare Part D plans that take drugs off their formularies during the course of a plan year to inform affected patients at least 60 days in advance.[9] Patients and their physicians were encouraged to develop and initiate transition procedures as soon as possible while trimethadione remained available. Over the following 12 months, routine written communications from the manufacturer regarding the status of drug availability accompanied each prescription refill. Prescription refill intervals were successively decreased from 90 to 30 day intervals to facilitate increased monitoring of the remaining drug supply and to encourage transition to other agents. Throughout, a key patient advocacy group, the Epilepsy Foundation, and an academic society, the American Epilepsy Society, were kept informed about the planned discontinuation of the trimethadione compassionate use program.

RESULTS

During the first six months of the transition program there was more than a 50% decrease in prescription refill requests and only a few medical information or external consultation requests were received. Twelve months following initiation of the transition program, trimethadione refill requests had significantly decreased to the point that only one refill request had been received within the last 60 days of the transition period. These results indicate that virtually all of the trimethadione recipients were able to transition to other therapies to manage their medical conditions. Since the manufacturer was blinded to these treatment decisions, specific data regarding current seizure diagnosis, medical

Trimethadione Transition Time Line

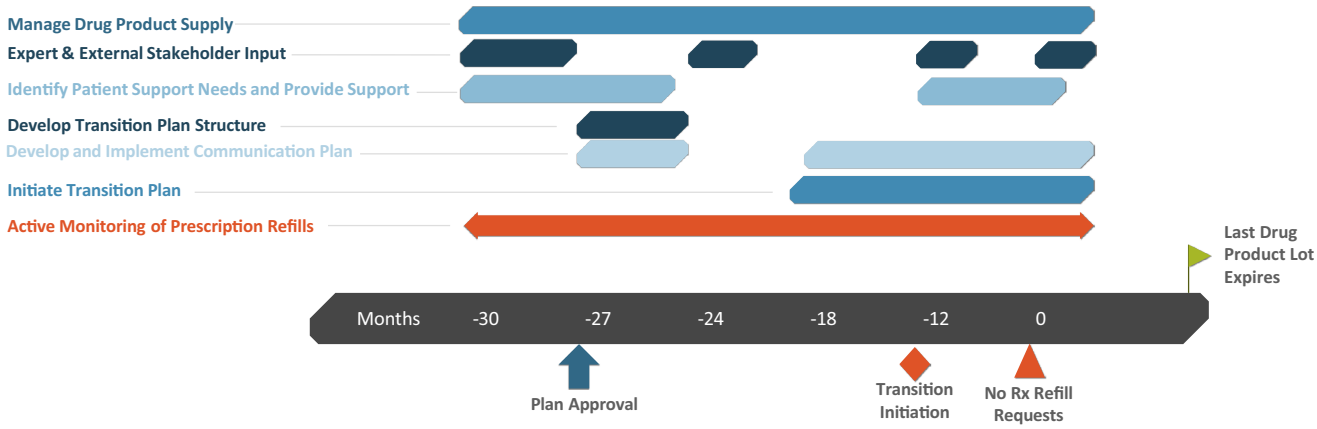

Figure 1 Summary of activities for the discontinuation of trimethadione. This timeline can serve as a model for discontinuation of other single source drugs and assumes an average time course for patient transition to an alternative therapy of approximately 6–12 weeks and a shelf life of available drug supply of approximately 3–4 years. This schematic is based on a designed 12-month transition phase for discontinuation of the approved drug. This timeline also incorporates sufficient time to capture internal and external stakeholder alignment of each phase of the transition process.

status, and therapeutic interventions are unavailable. Another aspect that supports the position that this transition program had minimal impact on patient care is the fact that there was a low frequency ($n = 1$) of consultations with the independent epileptologist. That said, the transition period afforded the attending physicians an opportunity to reassess their patients' neurological diagnoses, evaluate their general health status, and consider other viable therapeutic interventions based on current standards of care.

Figure 1 illustrates the planning and implementation timelines that were used for the discontinuation of trimethadione. This figure can serve as a model for discontinuation of an approved drug for which there is only a single manufacturer and a small patient population. A multitude of activities and events must be planned for and coordinated well in advance of the actual discontinuation period to ensure therapeutic continuity for and the support of patients. In the case of trimethadione, drug product supplies and their associated shelf-life expiry dates were carefully managed by the manufacturer to maximize utilization of the last available drug product lot. Once this drug product lot expires the manufacturer plans to request withdrawal of its New Drug Application.

SUMMARY AND CONCLUSION

At the time of its approval in 1946, trimethadione was considered an important advance in epilepsy therapy, especially for the management of absence seizures.[2] Over the next five decades, its medical utility as an antiepileptic agent diminished significantly such that by the mid-1990s only a single manufacturer was providing the drug to a limited number of patients.[7,8] Following its discontinuation from the market in 1995, the manufacturer continued to provide the drug on a compassionate use basis to a small number of trimethadione-experienced patients whose seizures were well controlled by the drug. This program continued for the next two decades until impending changes in the manufacturing site, process, and regulatory validation made continued supply of trimethadione no longer possible. This situation prompted the manufacturer to develop a structured and individualized plan for transitioning trimethadione patients, in consultation with their HCPs, to other appropriate therapies thus ensuring optimal use of the last available drug supplies. This plan, arrived at by the company and consulting bioethicists, consisted of multiple communications to these patients, their HCPs, advocacy groups, and medical societies. Additionally, prescribers were provided access to an independent epilepsy expert for consultations to assist them in developing effective therapeutic transition strategies. During the 12-month transition period, trimethadione prescription refill requests decreased by 98% and relatively few patient queries were received by the epilepsy specialists or the manufacturer. All have been satisfactorily resolved. These events suggest that the transition plan has enabled trimethadione patients to successfully convert to other appropriate antiseizure therapies. They also reveal the planning necessary to manage the termination of a compassionate access program that meets bioethics principles of fairness, nonmaleficence, and respect for persons.

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CONFLICT OF INTEREST
A.C.: I serve as the chair of the Compassionate Use Advisory Committees (CompAC), external panels of medical experts, bioethicists, and patient representatives formed by New York University (NYU) School of Medicine in collaboration with Janssen Pharmaceuticals. CompAC advises Janssen about requests for compassionate use of its investigational medicines. NYU receives administrative funding from Janssen to operate the CompAC committees, which includes arranging calls, managing initial requests, maintaining records, and paying for administrative staff. I am not paid for this activity, but money goes to the NYU School of Medicine Division of Medical Ethics, which I founded and run, to support committee infrastructure. I am an unpaid board member and senior fellow at GE2P2 Global Foundation, a United States–based nongovernmental organization with the mission to advance ethical and scientific rigor in research and evidence generation across health, human rights, humanitarian response, and development, and chair of its Independent Bioethics Advisory Committee (IBAC), which provides advisory support to biopharma organizations on expanded access programs, clinical trials, and in other areas. I am a paid member of an advisory board for Western IRB-Copernicus Group on human subjects research standards. In this role I discuss emerging issues in research ethics with WIRB/WCG leadership at meetings held three times a year. I also give lectures on research ethics topics to WIRB/WCG staff and fellows. The Division of Medical Ethics also has a grant from WIRB/WCG to provide education as part of an annual international research ethics fellows educational program held at NYU. I was a paid member of a US Food and Drug Administration (FDA)-mandated (data and safety monitoring board) on pediatric inhalers for asthma made by Merck, GlaxoSmithKline, and Novartis. A contract research organization paid a daily rate for work done. I have done legal work over the past two years for these law firms/organizations: St. Cloud Hospital legal department; Sedgwick LLP; The Cochran Firm, Washington, DC; Law Offices of Wade E. Byrd (plaintiff); Shipman & Goodwin LLP (Hanes v. Yale-New Haven Hospital, defense). I have given numerous speeches to academic and industrial audiences for which I was reimbursed for travel. J.R.T.: holds AbbVie and Abbott stock. H.P.B. and M.F.J. are employees of AbbVie, Inc. and hold AbbVie and Abbott stock.

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