Brand-to-Generic Substitution of Buprenorphine/Naloxone Sublingual Film in Puerto Rico: A Case Study

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A 56-year-old patient with a 1-year history of stable maintenance treatment with Suboxone for opioid use disorder (OUD) was switched to a generic formulation in May of 2019. The patient reported experiencing—over the course of the following 3 months—withdrawal symptoms when switched to the Alvogen-produced generic formulation in May of 2019 and then to the Sandoz-produced version in July of that same year, she also was positive for fentanyl during that time. As a result, the buprenorphine dose was increased, and the patient was stable at this new dose using the generic versions. Blood levels pre- and post-change (not reported in previous case reports) showed maximum buprenorphine concentration being reached more quickly when the brand-name drug was used. Additionally, the area under the curve (AUC) values indicate that the generic formulation had higher exposures than the brand-name drug. Based on the clinical impact of the brand-to-generic switch in this patient, further research in this area is warranted. In the meantime, clinicians should carefully monitor their patients so that, if warranted, dose adjustments can be made quickly and safely to minimize negatively impacting the OUD therapy outcomes of patients. [*P R Health Sci J 2021;40:192-194*]

Key words: Opioid use disorder, Brand to generic switch, Buprenorphine

Suboxone (buprenorphine/naloxone sublingual film) is indicated in the United States and Puerto Rico (PR) for the treatment of opioid use disorder (OUD) (1,2). In April 2019, the PR government healthcare plan, Plan Vital, changed its prescription formulary to cover only the generic sublingual films (approved by the US Food and Drug Administration [FDA] in 2018) and removed all coverage for the brand-name formulation (3). Afterwards, anecdotal reports began to surface of patients who had previously been stable using Suboxone but who were now experiencing withdrawal symptoms.

Case report

A 56-year-old female patient was initiated on treatment for OUD at a local government/Health Resources and Services Administration clinic in PR on June 6th of 2018. In addition to the drugs being taken to treat her OUD, the patient was also taking the following medications: rosuvastatin, 10 mg daily; omega-3 acid ethyl esters, 2 grams BID, fenofibrate, 145 mg daily; and Triumeq (abacavir/dolutegravir/lamivudine, 600 mg/50 mg/300 mg); and was using medicinal cannabis daily for generalized anxiety disorder. No changes were made to the above-mentioned medications throughout her treatment at the aforementioned clinic.

The patient began treatment for OUD with the brand-name drug buprenorphine/naloxone sublingual film (Suboxone) on June 6, 2018, starting with an initial dose of 16/4 mg once a day (Figure 1). The patient experienced no major setbacks for the next 6 months, never missed an appointment, evidenced no illicit drug use, and required no dose adjustments; no adverse effects were reported during this period.

In December of 2018, the patient reported experiencing withdrawal symptoms associated with depressive symptoms but with no illicit drug use, which led her provider to adjust her dosage of Suboxone (from 16/4 mg to 18/4.5 mg). The patient communicated that while she experienced symptoms of withdrawal/cravings she did not act on them by using any additional opioids. The patient thereafter remained, for the next 6 months (through May 2019) without further incident, on this new maintenance dose.

With the mandatory brand–generic change in April 2019 in PR, the patient was switched to generic formulations

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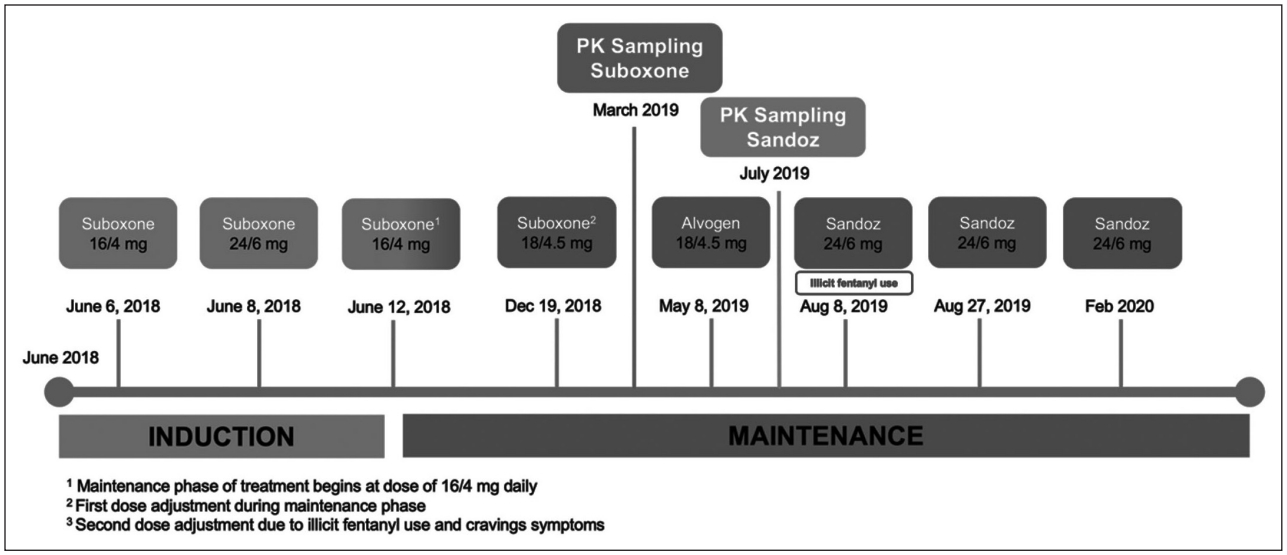

Figure 1. Timeline of the patient brand-to-generic substitution presented in this case report, starting when the patient was induced into treatment with Suboxone film and terminating with our last observation in February 2020.

manufactured by Alvogen and Sandoz. She was first prescribed Alvogen, and during a follow-up appointment at the clinic (May 8, 2019) reported feeling discomfort and having opioid cravings, asserting the new medication was less effective in calming her symptoms. She expressed feelings of desperation and fear that she would relapse into illicit opioid use. At this time, no dose adjustments were made. On August 8, 2019 (after 3 months of using the generic formulations—she had also received the Sandoz generic, of which more is written below), the patient's routine toxicology results were positive for fentanyl after the patient reported that, over the weekend, she had experienced intense withdrawal symptoms and had used fentanyl. The buprenorphine dose was then increased from 18/4.5 mg to 24/6 mg, daily. On August 27, 2019, the patient reported an improvement in her symptoms of withdrawal and cravings. Additionally, the patient reported in this appointment that the previous month (July), the generic formulation produced by Sandoz had been dispensed to her. She reported that, in her experience, Sandoz resulted in fewer adverse withdrawal symptoms and cravings. Following the most recent increase in August of 2019, the patient remained stable (as of February 2020) on the new dose of 24/6 mg using the Sandoz generic films.

This patient participated in a buprenorphine pharmacokinetic study. Her plasma levels of buprenorphine were initially measured prior to the brand–generic switch (March 2019), and repeat levels were obtained following the switch to the Sandoz generic formulation in July (before any changes in dosing were made). Over an 8-hour period, blood samples were collected, with the first sample being drawn as a trough prior to the morning dose administration. Of note, although the patient was prescribed 18/4.5 mg once daily, she reported consistently dividing her dose into 10/2.5 mg (morning) and 8/2 mg (evening).

A trough concentration was taken as the plasma level just before dosing, and the AUCs were estimated using the trapezoidal rule in Microsoft Excel, version 16.40. Table 1 shows that the Suboxone maximum/trough concentration ratio was more than double that of the generic. Additionally, following dose administration, the time to maximum concentration for the brand-name formulation was shorter (1 hour) compared to that of the generic formulation. The AUC of buprenorphine and its metabolites indicated higher exposure of the generic formulation compared to the brand.

Table 1. Pharmacokinetic values of buprenorphine after administration of brand-name (Suboxone) and generic (Sandoz) buprenorphine/naloxone formulations.

	Brand	Generic
C_{max}/C_o	7	2.6
Tmax (hrs)	1.97	3.00
BUP AUC (ng/mL * h)	22.5	26.95
BUP-G AUC (ng/mL * h)	2.16	3.84
n-BUP AUC (ng/mL * h)	5.49	6.84
n-BUP-G AUC (ng/mL * h)	20.13	36.78

Key: C_o, trough level; C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC, area under the curve.

Discussion

The several studies reporting on patients who experienced withdrawal/craving symptoms following a buprenorphine formulation switch mostly focused on the film-to-tablet change (4); few documented clinical observations of the brand-to-generic sublingual film switch have been made (5). In our case, it is interesting that the patient, whose symptoms worsened when she switched to the generic formulation, even though her exposure to the active drug was increased. A clinically important

observation of this case is the delayed maximum concentration of buprenorphine observed following the ingestion of the generic formulation, which may indicate a more gradual onset of drug exposure. Additionally, the differences between the maximum concentration/trough ratio values between these administrations suggests different absorption rates.

Most studies that report on brand–generic switches also report no apparent alterations in drug use by the patients after the change (4). However, these studies report that they used a flexible formulation switch, which allowed their patients to go back to the original formulation, with proper medical justifications. The patient described herein did report her use of fentanyl after having been forced to use the generic formulation for 3 months. The treating physician attempted several times to convince the administrators of the health plan to allow the patient to resume taking Suboxone but was unsuccessful. This event was a disruption of a previously stable treatment. This is consistent with other reports of increases in positive urine tests for illicit drugs in stable patients who experience insurance-mandated buprenorphine switches, with these patients feeling unhappy and anxious due to the lack of control over their treatment (6,7). Other clinics in PR have anecdotally observed patients experiencing withdrawal symptoms—and subsequently testing positive for illicit drugs—when those patients were switched to the generic film formulation. The case presented here is consistent with these anecdotal reports but adds the additional pharmacokinetic parameters for comparison.

A limitation of this case was the lack of withdrawal assessments, which limited our ability to accurately associate withdrawal symptoms with plasma levels. Given that this case is the first of its kind to be reported in PR, it is important that the proper clinical assessments for safe and effective brand–generic formulation substitutions be developed. In this case, a dose increase re-stabilized an OUD patient that acted on their withdrawal symptoms after a formulation switch by using illicit fentanyl. Although general clinical recommendations are unable to be developed based on the experience of this case, it is reasonable that patients switching from brand-to-generic formulations should be first informed about the change, and adjustments in their psychotherapy may help them cope with potential symptoms during this transition prior to dosing adjustments. The exact reason for these clinical and pharmacokinetic observations and why the patient did better while on the brand remains unclear; however it justifies the need for further systematic evaluations. In the meantime, clinicians and payers alike in PR should increase monitoring so that dose adjustments can be made quickly and safely, when warranted.

Resumen

Un paciente de 56 años en dosis fija de Suboxone (estable en tratamiento) para trastorno por uso de sustancias comenzó a utilizar formulaciones genéricas de Suboxone desde mayo 2019 debido a cambios en la cubierta de su plan médico. Durante los siguientes tres meses, la paciente reportó síntomas de retirada mientras tomaba dos versiones diferentes del genérico de Suboxone (Alvogen y Sandoz). Luego de tres meses, el paciente reportó síntomas intensos de retirada y uso ilícito de fentanilo. Como resultado su medico le aumento la dosis del genérico de buprenorfina para estabilizarlo. Niveles en sangre de buprenorfina mostraron diferencias en el tiempo para alcanzar la concentración máxima entre Suboxone y las genérica (Suboxone alcanzo la concentración máxima 1 hora antes que el genérico). El área bajo la curva indicó una mayor exposición a buprenorfina con el genérico, comparado con Suboxone. Basado en estas observaciones clínicas, se recomienda expandir este tipo de investigación para comprender mejor estas diferencias entre Suboxone y los genéricos en la poblacion.

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