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Effects of a Higher-Bioavailability Buprenorphine/Naloxone Sublingual Tablet Versus Buprenorphine/Naloxone Film for the Treatment of Opioid Dependence During Induction and Stabilization: A Multicenter, Randomized Trial

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ABSTRACT

Purpose: Sublingual buprenorphine and combination buprenorphine/naloxone (BNX) are effective options for the treatment of opioid dependence. A BNX sublingual tablet approved by the US Food and Drug Administration for the induction and maintenance treatment of opioid-dependence in adults was developed as a higher-bioavailability formulation, allowing for a 30% lesser dose of buprenorphine with bioequivalent systemic exposure compared with another BNX sublingual tablet formulation. No data were previously available comparing the higher-bioavailability BNX sublingual tablet to generic buprenorphine or BNX sublingual film; we therefore evaluated treatment retention during induction and stabilization with the higher-bioavailability BNX sublingual tablet versus generic buprenorphine or BNX sublingual film.

Methods: This multicenter, prospective, randomized, parallel-group noninferiority trial was conducted at 43 centers in the United States. Eligible patients were adults aged 18 to 65 years who met the criteria for opioid dependence and had at least mild withdrawal symptoms. On days 1 and 2, patients received blinded, fixed-dose induction with the higher-bioavailability BNX sublingual tablet or generic buprenorphine. On days 3 to 14, patients induced with BNX received open-label, titrated doses of the BNX tablet for stabilization; patients induced with buprenorphine received sublingual BNX film. Co-primary end points were treatment retention on days 3 and 15; noninferiority was concluded if the lower limit of the 95% CI of the between-group difference in treatment retention was $\geq -10\%$. Tolerability was assessed throughout the study period.

Findings: A total of 758 opioid-dependent patients were included in the study (BNX sublingual tablet, 383 patients; generic buprenorphine, 375). Day-3 retention rates were 93.9% (309/329) and 92.6% (302/326) with the BNX tablet and buprenorphine, respectively (between-group difference 95% CI, −2.6 to 5.1). Day-15 retention rates were 83.0% (273/329) and 82.5% (269/326) with the BNX tablet and BNX film, respectively (between-group difference 95% CI, –5.3 to 6.3). No unexpected tolerability issues were identified; the safety profile of the BNX sublingual tablet was similar to those of generic buprenorphine and BNX film.

Implications: Based on the findings from this study in patients with opioid dependence, the higher-bioavailability BNX sublingual tablet formulation was noninferior to both generic buprenorphine (induction) and BNX film (stabilization). These findings suggest that BNX sublingual tablets are an efficacious and well-tolerated option for induction and early stabilization treatment of opioid dependence. ClinicalTrials.gov identifier: NCT01908842. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮) © 2015 Published by Elsevier HS Journals, Inc.

Key words: buprenorphine, buprenorphine/naloxone combination, induction therapy, maintenance therapy, treatment retention.

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INTRODUCTION

Sublingual buprenorphine and combination buprenorphine/naloxone (BNX) are effective options for office-based treatment of opioid dependence.[1,2] Buprenorphine is a partial μ-opioid receptor agonist that promotes treatment retention, reduces illicit drug use, and relieves cravings in patients dependent on full μ-opioid agonists.[3] Unlike other partial opioid agonists, buprenorphine binds with high affinity to the μ-opioid receptor.[4] From a clinical perspective, the tight binding blocks the effects of exogenous opioids, which is important for the prevention of relapse. However, displacement of full μ-opioids by the higher-affinity partial agonist can lead to precipitated withdrawal,[5,6] which poses a clinical challenge during induction as patients transition from full μ-opioids. The μ-receptor antagonist naloxone is included in combination products to deter abuse, as it precipitates withdrawal symptoms when taken parenterally by opioid-dependent patients.[7,8] Naloxone has no or limited systemic effects when administered sublingually due to its low bioavailability via this route.[4]

The use of a BNX sublingual tablet formulation* was approved in 2002 by the US Food and Drug Administration for the treatment of opioid dependence in adults. Although the branded product was discontinued from the market, generic formulations remain available. Subsequently, a sublingual BNX film formulation† was approved in 2010 for use as maintenance treatment of opioid dependence in adults and in 2014 for the induction of treatment in those transitioning from short-acting opioids.[9,10] No BNX formulation is licensed for induction therapy in both patients dependent on long-acting opioids and patients dependent on short-acting opioids. The induction of therapy in patients dependent on long-acting opioids (eg, methadone) might be complicated by an increased risk for precipitated or prolonged withdrawal.[11–13] Limited clinical evidence exists regarding the efficacy of BNX film for induction in patients dependent on long-acting opioids, or among those transitioning from long-acting extended-release preparations.[14,15] Thus, buprenorphine monotherapy is the only treatment approved and recommended[11] for induction in patients transitioning from long-acting opioids. After successful induction, adherence of opioid-dependent patients to maintenance BNX therapy is important for preventing relapse and future illicit opioid use.[16] In addition, successful maintenance therapy might integrate psychosocial treatment to promote behavioral and/or lifestyle changes, as well as to address psychosocial challenges that might contribute to a patient's addiction.[9,11]

A higher-bioavailability BNX sublingual tablet formulation‡ was approved by the FDA in July 2013 for use as maintenance treatment in adult patients with opioid dependence and was made available for clinical use in September 2013. An indication for induction treatment in adult patients with opioid dependence followed in August 2015. This higher-bioavailability BNX sublingual product allows for the administration of a 30% lesser dose of buprenorphine with systemic exposure (ie, bioavailability) equivalent to that of a previously available BNX sublingual tablet formulation; the development of this tablet formulation also incorporated specific characteristics to address patients' preferences.[9] The technology used in the formulation, comprising micronized buprenorphine in an associative admixture with a citric acid buffer system, demonstrates rapid disintegration, an immediate but temporary reduction in pH, and synchronized buprenorphine release in vitro. These properties contribute to its increased dissolution rate and improved bioavailability.[17]

The clinical development of this higher-bioavailability sublingual tablet focused initially on comparisons to the previously available BNX tablet formulation. In a comparative bioavailability study in healthy participants who received naltrexone blockade, the use of a 5.7/1.4 mg dose of the BNX sublingual tablet (a 30% lesser buprenorphine dose) maintained bioequivalent buprenorphine systemic exposure[9] and 12% less naloxone exposure,[17] as well as significantly faster sublingual dissolve time ($P < 0.0001$),[9] compared with those of the other, 8/2-mg, BNX tablet.

Although these pharmacokinetic data on the higher-bioavailability BNX sublingual tablet[9] were sufficient for FDA approval, no published clinical studies have compared the effects of the BNX sublingual tablet formulation with either the generic buprenorphine sublingual tablet or BNX sublingual film. Given the importance of such data for guiding physicians' and patients' decision making, the clinical

*Trademark: Suboxone® (Reckitt Benckiser, Richmond, Virginia).

†Trademark: Suboxone® sublingual film (Reckitt Benckiser).

‡Trademark: Zubsolv® (Orexo US, Inc, Morristown, New Jersey).