Non-opioid Protocol for Opioid Detoxification and Transition to Antagonist Treatment

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A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2014

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Program Authorized to Offer Degree:

School of Public Health

Dedication:

I dedicate this thesis to my lovely family- my supportive husband Greg, my children Joelle and Nes, and my mother, who have inspired me to strive for commitment, earnestness and kindness while dedicating energy to public health. I feel humbled by the generous souls of my colleagues and patients, and in a way this thesis is an appreciation to all those touched by the opioid abuse epidemic.

University of Washington

Abstract

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Objective: The clinical effectiveness of a novel non-opioid and benzodiazepine-free protocol was compared to a standardized buprenorphine/naloxone (bup/nx) taper protocol for opioid detoxification and transition to subsequent relapse prevention strategies.

Methods: Retrospective chart review of DSM IV diagnosed opioid-dependent patients admitted for inpatient detoxification examined differences between 84 subjects that received a non-opioid protocol (treated with a scheduled 4-day regimen of tizanidine, hydroxyzine and gabapentin) and 40 subjects that received a 4-day bup/nx taper protocol. Both groups received ancillary medications and routine counseling. Primary outcomes were completion of detoxification, and facilitation to further chemical dependency treatment. Secondary outcomes included length of hospital stay, Clinical Opiate Withdrawal Scale (COWS) scores, ancillary medication use, adverse effects, and initiation of injectable ER naltrexone treatment.

Results: Non-opioid protocol subjects, as compared to subjects receiving the bup/nx protocol, had greater completion of detoxification (94% vs 80%, P= .026), and greater facilitation to further chemical dependency treatment (85% vs 63%, P = .006). The non-opioid protocol had a lower incidence of bradycardia (44% vs 65%, P = .035), and lower mean COWS scores on day 1 (3.3 vs 4.8; P < .001). No significant differences were observed between the two protocols for the average COWS scores on day 2, 3 and 4; rates of asymptomatic and symptomatic hypotension; reported adverse effects; length of hospital stay; and ancillary medication use (P > .05). In the non-opioid protocol 27 (32%) patients pursued transition to extended release naltrexone and 24 (89%) received the injection prior to hospital discharge.

Conclusion: This retrospective, non-randomized, case review study demonstrates the efficacy of a novel, non-opioid detoxification protocol using scheduled tizanidine, gabapentin and hydroxyzine for management of opioid withdrawal during the phase between cessation of opioids and initiation of relapse prevention strategies, including transition to injectable ER naltrexone.

Key Words: opioid withdrawal, opioid detoxification, antagonist therapy.

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I. Introduction

Over the last decade, there has been increasing public health, medical, and political attention paid to the escalation of prescribed and illicit opioid abuse and the rising national opioid epidemic. Aggressive prescribing of opioid analgesics (also called opioid pain relievers or prescription painkillers) has contributed to a dramatic increase in incidence of opioid use disorders and unintentional opioid mortality, leading to 16,917 (74% of the total drug overdose deaths) opioid overdose deaths in 2011 (1). Deaths from drug overdose have been rising steadily over the past two decades and have become the leading cause of injury death in the United States surpassing deaths involving motor vehicle accidents among people 25 to 65 years of age (1). The CDC estimates that in 2009 for every opioid related fatality there were 10 treatment admissions for opioid dependence, 32 ED visits for opioid abuse or misuse and 130 people who abuse or are addicted to opioid analgesics (2). In 2011, about 1.4 million ED visits involved the nonmedical use of pharmaceuticals, and among those, 420,040 visits were related to opioid analgesics (3). There has been increasing need for adoption of a public health approach to further outline prevention and intervention opportunities to opioid abuse and dependence, and its consequences, in order to foster solutions to this widespread problem.

Opioid dependence is a chronic medical condition and affects nearly 5 million people in the United States (4). Opioids subject to abuse and dependence include heroin, a universally illicit drug, and prescription opioid analgesics diverted for nonmedical use. Chronic abuse of and dependence on opioid drugs represents a critical public health and social problem, as well as a complex neurobiologic disorder for the affected individual

that often requires long-term treatment and care. Treatment of opioid dependence is critical to reduce its public health and social consequences, and to improve the well-being and social functioning of those affected. The main objectives of treating and rehabilitating persons with opioid use disorders are to reduce dependence on opioid drugs via pharmacologic and psychosocial interventions; to reduce the morbidity and mortality caused by, or associated with, the use of both legal opioid analgesics as well as illicit opioids, such as infectious diseases; to improve physical and psychological health; to reduce criminal behavior; to facilitate reintegration into the workforce and educational system; and, to improve social functioning and engagement.

Background and significance

In response to the continual rise in health and social costs related to the challenging and widespread opioid abuse epidemic, addiction medicine specialists and other physicians are often faced with the challenge of opioid withdrawal management as a first necessary treatment intervention for opioid dependence.

Opioid withdrawal is characterized by a pattern of signs and symptoms that develop after cessation of (or significant reduction in) heavy and prolonged opioid use (several weeks or longer), or after administration of an opioid antagonist after a period of opioid use (5). Safe and generally effective medication protocols for opioid detoxification are available in widely variable components. Providing adequate symptomatic relief from opioid withdrawal symptoms plays a key role during the early treatment phase following opioid cessation, allowing for engagement in behavioral interventions and potential transition to medication assisted treatment, such as buprenorphine maintenance substitution therapy,

or naltrexone antagonist therapy (6,7,8). Medication assisted treatment (MAT) is an evidence-based method that recognizes the physiological effects that prolonged opioid use can frequently have on a patient's homeostasis and overall functioning. Differing opioid and non-opioid pharmacotherapeutic approaches exist as short-term treatment modalities for treatment of acute withdrawal symptoms designed to ease this transition. Clonidine, an alpha-2 adrenergic agonist, reduces noradrenergic activity and noradrenaline release and has been accepted as a mainstay of non-opioid treatment for relief of withdrawal symptoms. However, Clonidine use presents limitations, such as variable control of anxiety, restlessness and craving, and problematic adverse effects of hypotension, bradycardia, dizziness, and sedation (9). Another medication used as a promising pharmacological tool in the treatment of opioid withdrawal is buprenorphine. Buprenorphine is a synthetic opioid medication, approved in the US for use in the treatment of opioid dependence in 2002, that displays unique pharmacology within the opioid class by attenuating withdrawal symptoms through its mu-receptor agonist action, and by decreasing the level of physical dependence through its kappa-receptor antagonist properties (10).

The use of buprenorphine is based on the principle of incomplete cross-tolerance in which one opioid is replaced with another and then slowly withdrawn (11,12). Buprenorphine is more effective than clonidine in reducing the signs and symptoms of opioid withdrawal, and retaining patients in detoxification treatment through completion (13). At the same time, however, as a long-acting synthetic opiate itself, buprenorphine can potentially contribute to post-acute withdrawal symptomatology after its use in detoxification is discontinued, which can prolong withdrawal symptoms and potentially

compromise successful early recovery (14).

Effective management of opioid withdrawal symptoms during the immediate transitional period between cessation of opioid use and initiation of medication assisted treatment (MAT) with naltrexone antagonist therapy is an increasingly common challenge. The path to addiction recovery is often complex, with significant risk for unsuccessful attempt(s) at cessation, if transition between opioid agonist abuse and antagonist treatment fails due to poorly executed opioid withdrawal management. This critical transition period may represent a barrier to recovery due to fear of withdrawal symptomatology, but may simultaneously provide an opportunity to improve outcomes, through increased treatment engagement due to patient desire for medical assistance with withdrawal management, and potential subsequent retention in continuing care. Inadequate control of acute withdrawal symptoms such as fatigue, insomnia, restlessness, muscle cramps, back pain, gastrointestinal distress, and anxiety could further lead to treatment failure. Some withdrawal protocols utilize benzodiazepines or other controlled substances, which can further delay or compromise the goal of addiction recovery by extending or creating physiologic dependence, and by inserting obstacles to getting to the next phase of chemical dependency treatment (15).

Recent research and clinical efforts have focused on improving the detoxification process and the transition from agonist to antagonist medications. A non-opioid and benzodiazepine-free protocol has advantages over opioid- based protocols, particularly if transitioning to opioid antagonist treatment (16). Adequate symptomatic relief from opioid withdrawal can play a key role in determining success or failure in the pre-

initiation stage of MAT with planned naltrexone antagonist therapy, and, when managed effectively, can contribute to successful early recovery (17).

Specific aims

The goal of the study is to examine the effectiveness of a novel combination of non-opioid/non-benzodiazepine medications for treatment of opioid withdrawal. This protocol may be of particular benefit for managing opioid withdrawal prior to initiation of naltrexone antagonist therapy or engagement in other relapse prevention strategies that do not utilize opioid substitution therapy. The clinical effectiveness of this novel non-opioid and benzodiazepine-free protocol was compared to a buprenorphine/naltrexone taper for opioid detoxification and transition to subsequent relapse prevention strategies. Initiation of extended release (ER) naltrexone treatment was one of the relapse prevention strategies sought by some of the patients in the non-opioid protocol group. Increasing the effectiveness of existing pharmacologic approaches to opioid detoxification would help facilitate successful implementation of MAT and available psychosocial interventions to opioid-addicted patients (18).

II. Methods

Study Design

This is a retrospective, non-randomized, case review study of data collected from January 1, 2011 to November 30, 2012 on opioid dependent subjects admitted to an inpatient detoxification facility at Addiction Recovery Service (ARS), Swedish Medical Center in

Seattle, Washington. The study compared the clinical effectiveness of a novel non-opioid and benzodiazepine-free protocol (utilized from November 1, 2011 to November 30, 2012) to a buprenorphine/naltrexone taper protocol (utilized from January 1, 2011 to October 31, 2011) for opioid detoxification and transition to subsequent relapse prevention strategies.

The chart review included subject assessment data, which was obtained both prior to and after the treatment had been initiated on the ARS medical floor, and was gathered by ARS medical and counseling personnel in routine fashion.

Study Population and Sample Selection

Study population included DSM IV diagnosed opioid-dependent patients seeking voluntary treatment and admitted for inpatient detoxification. Case eligibility was determined by an opioid dependence diagnosis, confirmed by an ICD code; voluntary participation; documented need of medical management of opioid withdrawal; medical and psychiatric appropriateness for non-opiate and/or buprenorphine detoxification treatment; negative pregnancy test (for all female patients); English language proficiency; and age 20- 55 years at the time of admission diagnosis. There were no enrollment restrictions based on gender, race, or ethnicity. The study did not include any vulnerable subjects with limited autonomy. Other exclusion criteria were polysubstance use, pregnant and lactating females, unstable medical status on admission, and planned induction to buprenorphine maintenance treatment. All subjects admitted to ARS were identified as opioid dependent by a certified chemical dependency professional. All

patients were eligible to receive ancillary medications, and underwent routine counseling. The Institutional Review Boards at the University of Washington and Swedish Medical Center approved the study.

Study Medication Protocols

Non-opioid detoxification protocol

The novel protocol is a combination of three scheduled medications during the 4-day hospital course, each targeting specific aspects of the typical opioid withdrawal syndrome that when combined have been observed to facilitate significant and adequate symptomatic relief. The first medication, ***tizanidine*** (dosage used in the protocol 8 mg Q6H) is a unique alpha-2 adrenergic receptor agonist that is structurally related to clonidine, but has a peripheral mechanism of action, as opposed to the central sympatholytic effect that clonidine provides. This produces milder cardiovascular effects relative to its strong potency as a skeletal muscle relaxant. It effectively reduces myalgias, tremor, muscle cramps, insomnia, sweating, diarrhea and anxiety (19,20,21). The second medication, ***gabapentin*** (dosage used in the protocol 300 mg TID and 600 mg HS) provides relief of muscle cramps, anxiety, insomnia, and restlessness during and potentially following detoxification (22, 23). It has been shown to attenuate the severity of withdrawal symptoms experienced by those physically dependent on opioid analgesics (24, 25, 26). The third medication is ***hydroxyzine*** (dosage used in the protocol 100 mg Q4H, hold for sedation), an H1 receptor antagonist that has anticholinergic and sedating effects that reduce anxiety, nausea and vomiting (27). Hydroxyzine acts on the D2 and

5HT2A receptor pathways when given in high doses to reduce dysphoria and anxiety (28). The non-opioid treatment protocol also included ancillary medications used as needed for relief of particular withdrawal symptoms, such as dicyclomine, acetaminophen, naproxen, loperamide, trazodone, clonidine and seroquel.

Buprenorphine/naloxone (bup/nx) taper protocol

The synthetic opioid buprenorphine has been used as a tool for opioid withdrawal management, since its approval by the FDA in 2002. In this study, a protocol utilizing standardized dosing of bup/nx was used as the control, and compared to the experimental non-opioid protocol over a range of outcome measures. The following regimen of bup/nx was provided: Day 1: 2 mg SL q2 h x 3, then 8mg SL BID; Day 2-3: 8 mg SL daily; Day 4: 4 mg SL given once. The bup/nx treatment protocol included the same ancillary medications, plus the skeletal muscle relaxant methocarbamol for symptomatic relief of specific withdrawal symptoms such as anxiety, restlessness, nausea, vomiting, diarrhea, and muscle, bone and joint pain and insomnia.

Measures

Primary outcomes

Primary outcomes measured were completion of detoxification, and facilitation to further formal chemical dependency treatment. Completion of detoxification was defined as the number of days from first dose of withdrawal medication to the last treatment dose received at the treatment facility, with completion of detoxification treatment determined by medical staff. Patients who left the hospital prior to completion of detoxification were

labeled as discharged against medical advice (AMA). Facilitation to further chemical dependency treatment was defined to include inpatient or outpatient participation in a formal, licensed chemical dependency treatment program.

Secondary outcomes

Secondary outcomes included length of stay (LOS), adverse effects/events, Clinical Opiate Withdrawal Scale (COWS) scores, ancillary medication use, and initiation of injectable ER naltrexone treatment. LOS was defined as the number of inpatient hospital days from admission to discharge at the treatment facility. COWS scores reflect a clinician-completed scale recorded in the hospital electronic system, that rates the presence/severity of 11 common opiate withdrawal signs or symptoms such as sweating, runny nose, etc). Ancillary medication use refers to the number of doses of available medications used in both detoxification protocols to facilitate management of opiate withdrawal symptoms on an as needed basis. Initiation of injectable ER naltrexone was defined by successful implementation of ER naltrexone antagonist therapy after oral challenge with Naltrexone; this outcome applies only to the non-opioid detox group.

Adverse events

Adverse effects were defined as *serious adverse events* that resulted in overnight hospitalization or death, were immediately life-threatening, or involved any permanent or substantially disabling event. *Medication-related adverse events* reported by participants assigned from each treatment group, including bradycardia (defined as documented HR<60 and/or symptomatically reported by the patient), asymptomatic (defined as documented BP<90/60 that was not felt by the patient) and symptomatic (defined as

documented BP<90/60 and/or symptomatically reported by the patient) hypotension, dizziness, and sedation.

Procedures

The participants were initiated on one of the 2 detoxification protocols over the hospital course of 4 days using standard detoxification procedures, including close patient observation by nursing, counseling interventions, and medical ARS staff evaluation. Subjects were assessed both prior to and after protocol medications were received. Documentation of scheduled distribution of protocol medications, and as-needed ancillary medication use, was performed. Patients were monitored for symptomatic and asymptomatic medication adverse effects, with assessment of vitals signs and COWS scores every 4 hours. Participants were permitted to remain in the hospital beyond the usual 4-day protocol time frame for an additional 24-48 hours if treatment for more severe opioid withdrawal was required. Patients in the non-opioid detox group were offered the option of initiating antagonist therapy with an oral naltrexone challenge followed by administration of injectable ER naltrexone during day 3 of hospital stay. There was no direct contact or post-discharge follow up with any of the identified study subjects.

Data Analysis

Subject characteristics were compared between the two treatment protocols using a two-sample t test, chi-square test and Fisher's exact test. Completion of detoxification and

discharge to further chemical dependency treatment was compared between the two treatment protocols using Fisher's exact test and exact logistic regression analysis, adjusted for potential confounders that included age, gender, education, occupation, marital status, smoking, family history of addiction, and chronic pain. Similarly, Fisher's exact tests and logistic regression analysis were used to compare the treatment groups on secondary (binary) outcomes and adverse events. Two-sample t tests and linear regression analysis, adjusted for potential confounders, were used to compare the two protocols on quantitative outcomes, which included average COWS scores, length of hospital stay and number of doses of ancillary medications. Sample size and power calculations were made based on the primary outcome measures. The sample sizes were calculated to demonstrate a 45% increase in the rate of completion of detoxification in the non-opioid detox protocol as compared to the bup-nx based protocol group (e.g., 80% vs 55% completion rate) with a 2:1 allocation ratio. A sample size of 79 subjects in the non-opioid protocol and 39 subjects in the bup/nx protocol was determined to provide 80% power based on chi-square test at 0.05 significance level (G*Power Version 3.1). All statistical tests utilized a two-tailed significance level of α=0.05. IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk NY, USA) and SAS Version 9.3 (SAS Institute Inc., Carey, NC, USA) were used to perform the data analysis.

III. Results

Subjects

A total of 324 non-opioid protocol subjects and 260 buprenorphine/naltrexone protocol subjects (bup/nx) were screened for the inclusion or exclusion criteria. There were 84 (25.9%) subjects in the non-opioid protocol and 40 (15.4%) in the bup/nx protocol that met the inclusion criteria for the study. Subjects with concomitant active substance use outside of opioids, such as alcohol, benzodiazepines, or stimulants, were excluded from the study in order to seek optimal sample purity for direct comparison of the effectiveness of the scheduled non-opioid medication protocol to the opioid agonist bup/nx protocol (Table 1). Of note, all subjects who were inducted to buprenorphine maintenance treatment via the non-opioid protocol were excluded from analysis.

Table 1. Reasons for exclusion in the non-opioid protocol and buprenorphine/naloxone (bup/nx) protocol.

Reason for exclusion	Non-opioid protocol (N = 240) % (n)	Bup/nx protocol (N = 220) % (n)
Age	12.4 (40)	19.2 (50)
Buprenorphine induction	0 (0)	16.9 (44)
Sedatives/hypnotics	25.3 (82)	25.0 (65)
Amphetamines/methamphetamines	7.0 (22)	2.3 (6)
Alcohol	4.9 (16)	4. 2 (11)
Sedatives/hypnotics and Amphetamines/methamphetamines	6.2 (20)	6.9 (18)
Alcohol and sedatives/hypnotics	5.6 (18)	2.3 (6)
Alcohol and Amphetamines/methamphetamines	4.3 (14)	1.5 (4)
Cocaine % (n)	1.5 (5)	0.4 (1)

Cocaine and sedatives/hypnotics	14.3 (12)	7.5 (3)
Cocaine and alcohol % (n)	0 (0)	0.4 (1)
Pregnant state % (n)	2.8 (9)	3.9 (10)
Medical comorbidities % (n)	0.6 (2)	0.4 (1)

Table 2. Characteristics of study participants in the non-opioid protocol and buprenorphine/naloxone (bup/nx) protocol.

Characteristic	Non-opioid protocol (N = 84)	Bup/nx protocol (N = 40)	P-value
Age (years), mean (SD)	27.24 (±8.21)	24.23 (±5.90)	.022
Gender, % (n)			.21
Female	38.1 (32)	50.0 (20)	
Male	62.0 (52)	50.0 (20)	
Education, % (n)			.36
>High school	48.8 (41)	40.0 (16)	
HSG/GED	51.2 (43)	60.0 (24)	
Employment			.072
Employed	54.8 (46)	37.5 (15)	
Unemployed	45.2 (38)	62.5 (25)	
Marital status, % (n)			.26
Married	17.9 (15)	10.0 (4)	
Single/divorced	82.1 (69)	90.0 (36)	
Chronic pain, % (n)	26.2 (22)	15.0 (6)	.16
Smoking status, % (n)			.14[1]
Never	23.8 (20)	12.5 (5)	
Former	2.4 (2)	2.5 (1)	
Current	71.4 (60)	80.0 (32)	
Chewing	2.4 (2)	1.6 (2)	
Pack-per Day, % (n)			.075
0-0.5	27.4 (23)	15.0 (6)	
0.5-1	42.9 (36)	35.0 (14)	
> 1	29.8 (25)	50.0 (20)	
Opiate history- % (n)			
Heroin	50.0 (42)	70.0 (28)	.036
Smoked	23.8 (20)	20.0 (8)	
Injected	26.2 (22)	50.0 (20)	
Oxycodone/Other	38.1 (32)	25.0 (10)	.15

Oral	14.3 (12)	10.0 (4)	
Smoked	15.5 (13)	10.0 (4)	
Nasal	8.3 (7)	5.0 (2)	
Prescribed	6.0 (5)	7.5 (3)	
Illicit	32.1 (27)	8.3 (7)	
Heroin/Oxycodone	17.5 (7)	5.0 (2)	.72
Methadone	3.6 (3)	0 (0)	.55
Prescribed	5.0 (2)	0 (0)	
Illicit	2.5 (1)	0 (0)	
Family history of addiction	64.3 (54)	55.0 (22)	.32

[1]Never smoking versus former, current or chewing.

The mean age for the non-opioid protocol group was 27 years compared to 24 years for the bup/nx protocol group (P= .022). A higher percentage (54.8 %) of the non-opioid group were employed, compared to 37.5% for the bup/nx group. The two protocol groups did not differ by gender, education, marital status, chronic pain, smoking status and family history of addiction. General retrospective data was taken on each subject's opiate use history. The non-opioid detox group reported higher incidence of illicit oxycodone use (38.1%) and mixed heroin/oxycodone use (17.5%), while the bup/nx group reported more heroin use (70% compared to 50% in the non-opioid group; P= .036). Neither mean daily dose, mean days of heroin, oxycodone or methadone use in the past 30 days, nor lifetime years of use, were collected as a component of routine data collection.

Primary Outcomes

Non-opioid protocol subjects had a greater completion of detoxification than subjects who received the bup/nx protocol (94% vs 80%; P = .026) (Table 3). A higher rate of detoxification completion in the non-opioid protocol was still found after controlling for

subject characteristics that included age, gender, education, occupation, marital status, smoking, family history of addition and chronic pain (Odds ratio = 5.0; 95% CI 1.2-20.3; P = .029). There was also a greater facilitation to further chemical dependency treatment for the non-opioid protocol than the bup/nx protocol (85% vs 63%; P = .006). The difference in facilitation to further chemical dependency treatment remained significant after controlling for subject characteristics (Odds ratio = 4.6; 95% CI 1.6-13.0; P = .004).

Table 3. Primary outcomes for the non-opioid protocol and buprenorphine/naloxone (Bup/nx) protocol.

	Non-opioid protocol (N = 84)		Bup/nx protocol (N = 40)		
Variable	% (n)	95% CI	% (n)	95% CI	P[1]
Completion of detoxification/AMA	94.0 (79)	86.6-98.0	80.0 (32)	64.3-90.0	.026
Discharge to chemical dependency treatment	84.5% (71)	74.9-91.5	62.5 (25)	45.8-77.3	.006

[1]Fischer's exact test, p-value.

Secondary outcomes and adverse events

Withdrawal symptoms

To characterize the effectiveness of both detoxification protocols, individual COWS scores were compared between the non-opioid group and the bup/nx group. The non-opioid protocol had lower mean COWS scores on day 1 (3.3 vs 4.8; P < .001) (Table 4).

No significant differences were observed between the two protocols for the average COWS scores on day 2, 3 and 4 ($P > .05$). In the non-opioid protocol 27 (32%) patients pursued transition to oral naltrexone challenge and extended release naltrexone and 24 (89%) received the injection prior to hospital discharge without medication-precipitated withdrawal. One patient (3.70%) reported precipitated withdrawal symptoms from the oral naltrexone challenge and was given medication to assist with symptom relief.

Length of stay (days) and use of ancillary medications

No significant differences were observed between the two protocols for the average length of hospital stay, or ancillary medication use ($P > .05$) (Table 4). The mean LOS for the non-opioid group was 3.57 days compared to the bup/nx group of 3.38 days. The sample size for both groups decreased significantly during hospital day 4 with non-opioid group of n=49 and bup/nx n=21, and during hospital day 5 with non-opioid group n=13 and bup/nx n=7; the remainder of the patients completed treatment prior to day 4 and were discharged. All subjects received ancillary medications as needed to facilitate opioid withdrawal management. There were no significant differences in either the mean daily dose of each individual ancillary medication administered, or in the mean of total doses of ancillary medications in aggregate that were administered to the two groups during the detoxification treatment.

Table 4. Secondary outcomes for the non-opioid protocol and buprenorphine/naloxone (Bup/nx) protocol.

	Non-opioid protocol	Bup/nx protocol

Variable	(N = 84) Mean (SD)	Range	(N = 40) Mean (SD)	Range	P[1]
Clinical Opiate Withdrawal Scale (COWS)					
Day 1	3.3 (2.0)	0.0 – 8.3	4.8 (1.9)	1.2 – 10.0	<.001
Day 2	3.3 (1.9)	0.0 - 10.8	3.2 (1.8)	0.0 - 7.0	.59
Day 3	2.8 (1.7)	0.0 - 7.8	2.1 (1.7)	0.0 - 6.0	.083
Day 4	2.4 (1.6)	0.0 - 6.0	1.9 (1.6)	0.0 – 5.6	.23
Day 5	2.6 (1.6)	0.0 – 6.0	1.5 (1.5)	0.0 – 4.0	.15
Length of stay (days)	3.6 (1.0)	1 – 6	3.4 (1.4)	1 – 7	.42
Number of doses of ancillary medications	11.6 (7.4)	0 – 36	11.8 (8.2)	0 – 37	.62

[1]Two-sample t test, p-value.

Adverse events

There were no serious adverse events and no medication-related adverse events that resulted in discontinuation of treatment and/or preliminary discharge from the detoxification unit. Two patients in the non-opioid group arm (n=2, 2.38%) reported sedation that was thought to be (but not confirmed) related to gabapentin, and two patients of the bup/nx group (n=2, 5.0%) reported dizziness that was thought most likely to have been related to clonidine. Of note, clonidine was offered as an ancillary medication to the non-opioid group also, and there were no recorded episodes of dizziness in the group. The non-opioid protocol had a lower incidence of bradycardia (44% vs 65%, P = .035). No significant differences were observed between the two protocols for rates of asymptomatic and symptomatic hypotension, sedation and dizziness (P > .05) (Table 5). All secondary outcome results did not change after adjusting for age,

gender, education, occupation, marital status, smoking, family history of addiction, and chronic pain. There was no direct contact or follow up with any of the study subjects.

Table 5. Adverse events for the non-opioid protocol and buprenorphine/naloxone (Bup/nx) protocol.

Variable	Non-opioid protocol (N = 84) % (n)	Bup/nx protocol (N = 40) % (n)	P[1]
Hypotension	26.2 (22)	35.0 (14)	.32
Symptomatic hypotension	8.3 (7)	10.0 (4)	.75

[1]Fischer's exact test, p-value.

Transition to MAT with ER naltrexone

A total of 27 (32%) patients in the non-opioid protocol arm pursued transition to ER naltrexone, and were first given an oral Naltrexone challenge of 25 mg; 24 (89%) of them then received the extended-release injection prior to hospital discharge, without any noted significant withdrawal symptoms or adverse effects. Three patients received the oral Naltrexone challenge and did not move forward with the IM injection. Two of these patients tolerated the oral Naltrexone dose well, but decided for their own reasons that they would prefer to be discharged from the hospital without starting ER naltrexone. The third patient experienced precipitated withdrawal following the oral challenge on hospital day 4, which may have been due to taking methadone, a long-acting opioid, prior to hospital admission. The patient was treated with medications to manage the precipitated opioid withdrawal symptoms, and elected to discharge without having received the ER naltrexone injection.

IV. Discussion

This is the first study to directly compare an experimental non-opioid detoxification protocol with scheduled tizanidine, gabapentin and hydroxyzine to an opioid substitution approach utilizing a bup/nx taper protocol. Consistent with previous research, the study is predicated on Cochrane reviews of buprenorphine for the management of opioid withdrawal, and other opioid detoxification approaches (9). It could be argued that the relatively small sample sizes are unlikely to offer sufficient statistical power to demonstrate significant differences between the two detoxification protocols. However, it was felt that direct comparison of smaller but more consistent and pure opioid-dependent samples would produce more definitive findings in the context of direct comparison between the two detoxification protocols, which could warrant a future larger and more controlled study, if the data supported the hypothesis.

This study found that by the two primary outcomes, the non-opioid protocol was superior to the bup/nx taper protocol. Study subjects who were treated with this protocol had greater rates of completion of detoxification (P= .029) and facilitation to further chemical dependency treatment (P= .004) than the bup/nx taper group. Patients who were treated with the non-opioid protocol had a 3.95 times greater likelihood of completing detoxification compared to the bup/nx group when adjusted to age, gender, education, occupation, marital status, smoking, family history of addiction, and chronic pain. The non-opioid group had a 3.28 times greater likelihood of moving on to further engagement in formal chemical dependency treatment in comparison to the bup/nx group when

adjusted to age, gender, education, occupation, marital status, smoking, family history of addiction, and chronic pain. Both protocol regimens were well tolerated. The combination of the three medications in the non-opioid protocol provided better symptom relief, with a lower mean COWS scores on day 1 ($P < .001$), when compared to the bup/nx taper protocol. This is of very important clinical significance, as the first 24 hours of withdrawal management following cessation of opioids critically influences completion of detoxification and treatment retention. Introduction of bup/nx for withdrawal management is often delayed based on time of last opioid use, which could represent a potential negative influence on treatment engagement if patients have not received adequate symptom relief during that transitional time period. This difference may have accounted for the statistically lower COWS scores on day 1 for the non-opioid group. No significant difference was found in mean COWS scores on day 2, 3 and 4, which speaks to the adequate symptom relief achieved by the non-opioid protocol when directly compared to the long-acting opioid agonist activity of bup/nx. There were no serious adverse events and no AMA discharges related to adverse medication effects reported with either regimen. The most common adverse events recorded were bradycardia, asymptomatic and symptomatic hypotension. The non-opioid protocol was superior in lower incidence of bradycardia ($P = .040$) and non-inferior in asymptomatic and symptomatic hypotension, LOS, and mean dose of total ancillary medication use. The study partially addressed unresolved questions from previous studies regarding what constitutes a safe and effective dose of buprenorphine for acute detoxification, and used dosing similar to the range addressed in Gowing et al, 2009 and in Oreskovich et al, 2004. The bup/nx protocol doses were well tolerated by the study participants.

The experimental non-opioid protocol would appear to offer substantial clinical advantages in facilitating safe and efficacious transition to MAT and opioid antagonist treatment, as well as behavioral relapse prevention strategies such as formal chemical dependency treatment. It supports and amplifies recent research and clinical efforts to offer more effective opioid withdrawal management with successful transition to MAT with antagonist treatment. The non-opioid protocol provided comfortable and safe strategy for detoxification and transition from opioid agonist to antagonist treatment with 24 (89% of all subjects pursuing ER injection) successfully receiving the ER injection.

This study has several limitations. This was not a randomized controlled study. Its retrospective design did not allow for direct temporal comparison between the two groups. The study excluded all other active substance and polysubstance-using patients, resulting in smaller sample groups with decreased statistical power. The samples were, however, more consistent and pure, and therefore more directly comparable in expectations for opioid withdrawal management.

By demonstrating this novel non-opioid and non-benzodiazepine detoxification protocol, the study offers the treating clinician a useful tool to address the varied needs of the increasing population of opioid-dependent individuals seeking treatment.

V. Conclusions

Successful opioid detoxification and transition to MAT allows patients to stabilize physiologically and psychologically within days, ceasing the pattern of rapid fluctuations in opioid blood levels and associated withdrawal symptoms that short-acting opioids like

heroin and many prescription drugs create. The findings of this study demonstrate that this novel non-opioid non-benzodiazepine protocol utilizing scheduled tizanidine, hydroxyzine and gabapentin was more effective in the management of opioid detoxification compared to a protocol using opioid substitution therapy with bup/nx, when assessing completion of detoxification and facilitation to formal chemical dependency treatment and other interventions aimed at promoting a recovery-oriented lifestyle. Further, it allowed for efficient introduction to oral antagonist therapy during the opioid detoxification period and transition to MAT with antagonist injectable ER naltrexone. Future controlled, prospective studies are warranted comparing the effectiveness of this non-opioid protocol to other existing protocols for acute opioid detoxification and transition to MAT with antagonist treatment, in both inpatient and outpatient settings.

Acknowledgements:

The author would like to thank Lloyd Mancl, the thesis chair, who has provided compassionate guidance and support; The Institutional Review Boards at the University of Washington and Swedish Medical Center; and, colleagues and patients who have made this study possible.

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