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Serotonin Syndrome and/or Opioid Withdrawal after the First Dose of Naltrexone HCl/Bupropion HCl: an Observational Study

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THESIS

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Serotonin Syndrome and/or Opioid Withdrawal Occurring after the First Dose of Naltrexone HCl/Bupropion HCl with Concomitant Use of an Opioid: an Observational Study

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ABSTRACT

In 2014, the Food and Drug Administration approved naltrexone HCl/bupropion HCl, a combination of an antidepressant and an opioid antagonist for chronic weight management therapy. Concurrent use of antidepressants and opioids has the potential to cause drug interactions involving serotonin syndrome. Our primary objective is to identify cases of serotonin syndrome and/or opioid withdrawal after initiation of naltrexone HCl/bupropion HCl. Our secondary objective is to assess which specific opioids are more likely to cause a drug interaction with naltrexone HCl/bupropion HCl. We performed an observational study by reviewing cases in the RADARS® database from January 2014 through December 2018. The cases considered must have taken their first

dose of naltrexone HCl/bupropion HCl with concomitant use of an opioid, and met the inclusion criteria. Cases were determined to involve serotonin syndrome and/or opioid withdrawal using Hunter's Serotonin Toxicity Criteria and the Clinical Opioid Withdrawal Scale. The primary outcome measures were total number of cases with at least a moderate outcome, total number of cases determined to experience serotonin syndrome and/or opioid withdrawal and total number of cases to experience serotonin syndrome and/or withdrawal with at least a moderate outcome. The secondary outcome measures included the frequency of different opioids involved, benzodiazepine administration, and supportive care with either mechanical ventilation or intubation. Thirty-three cases in RADARS® met inclusion criteria, and 23 cases contained results for medical outcome. The 23 cases followed to medical outcome resulted in two major effects, 14 moderate effects and seven minor effects. Sixteen out of 23 cases (70%) had at least a moderate outcome. Seventeen out of 23 cases (74.0%) experienced serotonin syndrome and/or withdrawal. Overall, 13 out of 17 cases (76.5%) experienced serotonin syndrome and/or withdrawal and resulted in at least a moderate outcome. This study suggests occurrence of a drug interaction in the form of serotonin syndrome and/or opioid withdrawal with at least a moderate outcome after the first dose of naltrexone HCl/bupropion HCl while on opioid therapy.

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Background

In 2015-2016, the prevalence of obesity in U.S. adults was 39.8% according to the CDC.[1] The National Health and Nutrition Examination Surveys, from 2005-2010 reported 43.2% of obese adults also suffered from depression as compared to 33% who did not.[2] In 2014, a study by Miller *et al*. showed 15% of patients with chronic pain also suffered from depressive disorder. Of the patients with chronic pain, 16% filled an opioid alone and 28% filled both a nonopioid and opioid as chronic pain management therapy. The most common nonopioid medications used for pain management were non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressants.[3] These percentages show that antidepressant medications are likely used alone or concurrently with opioids by patients who are obese or have chronic pain. Naltrexone HCl/bupropion HCl is a chronic weight management therapy consisting of an opioid antagonist and antidepressant.[4] Naltrexone HCl/bupropion HCl, used by over 800,000 patients in the U.S. is the most prescribed medication for weight loss.[5] The medication was approved for adults in 2014; it was indicated for patients with a body mass index of 30 kg/m^2 or greater or 27 kg/m^2 or greater plus at least one of the following: hypertension, type 2 diabetes, or dyslipidemia.[4] Since this drug has only been on the market for four years, there are no significant data published on adverse effects. In the FDA approval process, adverse effects are a critical aspect. The package insert clearly states the potential for drug interactions and the risk of experiencing opioid withdrawal while taking naltrexone HCl/bupropion HCl with concomitant opioid use; however, it does not mention the risk for

serotonin syndrome. It is important to investigate the occurrence and medical outcome of this interaction.

Serotonin, or 5-hydroxytryptamine, is a neurotransmitter that can act both centrally and peripherally; it is released from neurons in various regions of the brain and the enterochromaffin cells of the gastrointestinal tract. Serotonin is released from the lower pons and medulla, controlling nociception, wakefulness, thermoregulation, attention, emesis, appetite, affective behavior, and motor tone.[6,7] Peripherally, it stimulates vasoconstriction, uterine contraction, bronchoconstriction, gastrointestinal motility, and platelet aggregation.[7] Serotonin syndrome is known to cause a triad of signs and symptoms involving altered mental status, autonomic hyperactivity, and neuromuscular abnormalities with variable severity.[6] The diagnosis includes evaluation of medical history, physical and neurological exam, and the patient's list of medications taken within the last two months. Due to a plethora of signs and symptoms and the range of severity in clinical effects, multiple attempts have been made to develop diagnostic criteria. Sternbach originally derived his criteria in 1991 from 10 case reports and two case series.[7] Patients met this criterion by showing three of the ten common clinical effects, along with use or dose increase of a serotonergic agent, and absence of a neuroleptic agent.[7] Radomski later reviewed 24 cases from 1991 to 1995 and classified the cases into a mild state of serotonin related symptoms, serotonin syndrome, or a toxic serotonergic state.[8] Shortly after, he Hunter group formulated a decision rule criterion by univariate and multivariate analysis of a dataset of selective serotonin reuptake inhibitor (SSRI)-alone

overdoses and a test dataset of all serotonergic medication overdoses from 1987 to 2002.[9] Currently, Hunter's Criteria is the preferred method for diagnosis. Table 1 shows Hunter's Criteria.[9]

Table 1

Hunter Serotonin Toxicity Criteria: Decision Rules
In the presence of a serotonergic agent: serotonin toxicity occurs 1. IF spontaneous clonus = yes 2. OR IF inducible clonus = yes AND agitation = yes OR diaphoresis = yes 3. OR IF ocular clonus = yes AND agitation = yes OR diaphoresis = yes 4. OR IF tremor = yes AND hyperreflexia = yes **5.** OR IF hypertonia = yes AND temperature > 38˚ C AND ocular clonus = yes OR inducible clonus
Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003 Sep;96(9):635-42

Serotonin syndrome is a predictable manifestation that 85% of physicians are unaware of or tend to overlook.[10,11] It may occur after therapeutic use, increased dose, or overdose of a single serotonergic agent, after concomitant use of multiple serotonergic agents, or by complex drug interactions triggering various mechanisms of serotonergic stimulation.[7] It can be caused by an increase in release of serotonin, an increase in the synthesis of serotonin, direct receptor stimulation, inhibition of serotonin reuptake, or decreased metabolism.[7,12,13] There are 7 types of serotonin receptors (5-HT1 to 5-HT7) with the main subtypes involved in serotonin toxicity being 5-HT1A and 5-HT2A.[13,11] Along with the main mechanisms leading to excess serotonergic excitation, there are pharmacogenomic factors that may predispose individuals to serotonin syndrome including: variants of isoforms CYP2D6 and CYP3A4, hypersensitivity from spliced gene variants, and allele polymorphisms.[14] Inhibition of norepinephrine reuptake, blockage of NMDA and GABA, and antagonism at 5-HT3 have also been associated as indirect mechanisms of excess serotonin in animal models.[13]

Antidepressants are the most common medication involved in serotonin cases. Of the various combinations of drugs that result in pharmacodynamic interactions, serotonin reuptake inhibitors and opioids are the most common culprit to contribute to this syndrome.[15] Selective serotonin reuptake inhibitors (SSRIs) such as citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, and paroxetine bind to serotonin reuptake transporters, prevent reuptake in the synaptic cleft, and inhibit CYP2D6 pathways.[6] Serotonin and norepinephrine

reuptake inhibitors (SNRIs), like venlafaxine, also prevent reuptake.[16] Tricyclic antidepressants (TCAs) with a tertiary amine group, such as amitriptyline, imipramine, and clomipramine strongly block serotonin and norepinephrine reuptake and desensitize 5-HT, making the tertiary amine TCAs more prone to cause serotonin syndrome.[17] Monoamine oxidase inhibitors (MAOIs) inhibit serotonin metabolism.[18] The mechanism of serotonin syndrome from bupropion is less clear.

Naltrexone HCl/bupropion HCl is a combination of a competitive opioid antagonist and an amino ketone antidepressant. Naltrexone, which binds to mu, kappa, and delta opioid receptors, has a great affinity for opioid receptors and may prevent or displace opioid agonists from binding to the receptor. Bupropion selectively inhibits neuronal uptake of dopamine and norepinephrine with indirect effects on serotonin receptors. Bupropion and its active metabolite are both inhibitors of CYP2D6, which may affect the metabolism of other drugs in the body. Bupropion inhibits catecholamine reuptake activity. In rats, studies have shown significant firing activity of serotonergic and noradrenergic neurons after continuous administration of 30 mg/kg bupropion.[19] Although the serotonergic activity of bupropion may not be considered a direct mechanism, its inhibition of CYP2D6 plays an indirect role in serotonin toxicity. Bupropion and its main metabolite, hydroxybupropion, both inhibit this isoenzyme pathway leading to increased levels of other drugs, such as SSRIs, TCAs and some opioids.[20,14,21] As of March 2019, there are at least 12 published cases of serotonin syndrome

involving bupropion (Table 2).[12,21-31] Two reports were caused by bupropion alone and four involved concurrent opioid use.[22,28,23,25,27,30]

Table 2

Cases of Serotonin Syndrome Involving Bupropion			
Medications	**Age/Sex**	**Outcome**	**Reference**
Bupropion	15 M	Major	Thorpe, 2010
Bupropion, ondansetron, paroxetine, duloxetine	68 F	Major	Gollapudy, 2012
Bupropion, tramadol, trazodone, oxycodone	62 M	Moderate	Falls, 2014
Bupropion, trazodone, quetiapine	70 F	Moderate	Cheng, 2015
Bupropion, sertraline	62 F	Moderate	Munhoz, 2004
Bupropion, tramadol, citalopram	62 M	Moderate	Shahani, 2012
Bupropion, fluoxetine, trazodone, olanzapine, risperidone,	24 M	Moderate	Little, 2018
Bupropion, fluoxetine, olanzapine, methadone	53 F	Major	Dvir, 2007
Bupropion	43 M	Moderate	Szala;y, 2008
Bupropion, sertraline, trazodone, linezolid, lithium	45 M	Major	Lavery, 2001
Bupropion, duloxetine, cyclobenzaprine, oxycodone	53 M	Moderate	Keegan, 2006
Bupropion, paroxetine, atomoxetine	55 M	Major	Muzky, 2010

The phenylpiperidine derivatives and synthetic piperidine opioids are considered to have weak serotonergic activity via serotonin reuptake inhibition and increased intrasynaptic release through gamma amino butyric acid (GABA) inhibition. This class includes meperidine, tramadol, methadone, fentanyl, dextromethorphan, tapentadol, and propoxyphene.[12,32] The phenanthrene morphine analogs are not considered to be serotonin reuptake inhibitors, but may increase intrasynaptic serotonin levels indirectly; they include morphine, oxycodone, hydromorphone, oxymorphone, and buprenorphine.[13] In any case, each drug possesses unique characteristics that may promote serotonin stimulation (Table 3). In an *in vitro* study of human transporter-transfected HEK293 cells, dextromethorphan inhibited SERT (the monoamine transporter of 5-HT) at the same degree as fluoxetine, methadone, and meperidine to a slightly less degree, and tramadol, tapentadol and O-desmethyltramadol (the M1 metabolite of tramadol) weakly at therapeutic concentrations. The only opioid that possessed relevant binding affinity for 5-HT1A was fentanyl; however, methadone, meperidine, and fentanyl showed relevant binding for 5-HT2A (Table 3).[33] According to a literature review in 2016, tramadol, meperidine and methadone are the most common opioids involved in serotonin syndrome.[34,35]

Tramadol is a partial opioid agonist and substrate of CYP2D6. It has a more potent active metabolite that binds to the mu opioid receptor, and is a substrate of CYP3A4.[14] Tramadol inhibits neurotransmitter reuptake and has been associated with serotonin syndrome when used with fluoxetine, citalopram, sertraline, escitalopram, paroxetine, venlafaxine, mirtazapine, bupropion,

oxycodone, and trazodone.[20,14] Tramadol has also been reported as the most frequent opioid involved in serotonin syndrome and serotonergic fatality.[36]

Meperidine is a mu and kappa opioid agonist and a substrate of CYP2B6, with an active metabolite normeperidine. It also inhibits serotonin reuptake and has 5-HT2A agonism. It has been associated with serotonin syndrome, alone or with another contributing agent, such as chlomipramine, phenelzine, fluoxetine and citalopram.[20,36]

Methadone, a synthetic opioid and a racemic mixture of levomethadone and dextromethadone, is slowly metabolized by enzymes CYP3A4, CYP2B6, and CYP2D6, and acts as a substrate of P-glycoprotein. Levomethadone is an inhibitor of NMDA.[20] Cases of methadone causing serotonin toxicity have been reported with co-administration of tramadol, paroxetine, citalopram, fluoxetine, phenelzine, fentanyl, duloxetine, venlafaxine, and ciprofloxacin.[34,36]

Table 3

Opioid Characteristics				
Drug	**Mechanism of serotonergic activity**	**Substrate**	**Inhibitor**	**Receptor agonist activity**
Tramadol	Inhibits serotonin reuptake Increased serotonin release	CYP2D6 CYP3A4		
Fentanyl	Inhibits serotonin reuptake, Inhibits efflux of 5-HT Activates serotonin receptor	CYP3A4, P-gp		5-HT1A 5-HT2A
Methadone	Inhibits serotonin reuptake Increased serotonin release Activates serotonin receptor	CYP3A4, CYP2B6, CYP2D6 P-gp	CYP2D6	5-HT2A
Meperidine	Inhibits serotonin reuptake Activates serotonin receptor	CYP2B6		5-HT2A
Morphine	Indirect	CYP3A4 P-gp		
Oxycodone	Indirect	CYP3A4, CYP2D6		
Tapentadol	Inhibits serotonin reuptake	CYP2C9 CYP2C19 CYP2D6		
Dextromethorphan	Inhibits serotonin reuptake Increased serotonin release	CYP2D6 CYP3A4		
Buprenorphine	Indirect	CYP3A4 P-gp	CYP2D6 CYP3A4	
Hydrocodone	Indirect	CYP2D6 CYP3A4		
Hydromorphone	Indirect			
Oxymorphone	Indirect			
Bupropion	Indirect	CYP2B6 CYP3A4 CYP2C19	CYP2D6	

Methods

Post-marketing surveillance for prescription opioids is available through The Researched Abuse, Diversion, and Addiction-Related Surveillance System (RADARS).[37] This system is a subsidiary of Denver Health and Hospital Authority, funded by subscriptions from pharmaceutical manufacturers, government, and non-government agencies. RADARS provides a mosaic strategy surveillance system for monitoring of newly approved drugs by collecting product-and-geographically specific data on abuse, misuse, and diversion of prescription drugs for research and reporting services. This system allows RADARS to provide services such as post marketing surveillance, epidemiological studies, advisory board participation, and advisory committee consultation. There are 51 out of 55 poison centers in the U.S. that partner with RADARS to provide weekly detailed exposure cases involving prescription opioids. RADARS methods have been published previously.[38] We investigated cases of naltrexone HCl/bupropion HCl taken along with an opioid, reported to RADARS by participating poison centers. Poison center cases in the RADARS' database include de-identified case notes as well as data captured in standardized fields used by the National Poison Data System.[39] Field definitions for substance and clinical effects are published by the American Association of Poison Control Centers.[39] Our database review searched for cases occurring from January 2014 to December 2018. Eligible cases included all human exposure cases where a prescription opioid from the RADARS list and naltrexone HCl/bupropion HCl were included in the substance field. RADARS

personnel identified eligible cases using the search field for prescription opioids captured in RADARS (buprenorphine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, tapentadol and tramadol) who also took their first dose of naltrexone HCl/bupropion HCl.[37,39] Exclusion criteria were information cases, animal exposures, subjects under the age of eighteen, and subjects who were pregnant or incarcerated. Each case was assessed for case notes and clinical effects that were consistent with published criteria for terms used in diagnosis of either opioid withdrawal or serotonin syndrome (Appendix A).[40] Clinical effects captured in the case notes that reflected opioid withdrawal or serotonin syndrome were searched for via text search using the terms provided in the (Appendix A) and their synonyms. RADARS personnel collected the following information for each case: reason for exposure: opioid formulation, name and dose, dose of naltrexone HCl/bupropion HCl, duration of exposure, medical outcome, sex, age, exposure acuity, onset of symptoms, generic code for other medications involved, and year. NPDS was used to define terms used to capture demographics, reason for exposure, drugs involved, route of administration, and medical outcome (Appendix B). RADARS assigned unidentifiable codes for each case securely transferred the data to the New Mexico Poison and Drug Information Center using our approved Data Use Agreement. Two pharmacists reviewed the de-identified cases to assure there were no discrepancies in determining who experienced serotonin syndrome and/or opioid withdrawal by using Hunter's Serotonin Toxicity Criteria and the Clinical Opioid Withdrawal Scale (Appendix C).[40] In the case of a discrepancy, a

medical toxicologist would act as the third individual to review the case and make the final diagnosis. These methods were used to collect data for our outcome measures.

Our primary outcome measures included the following: cases with at least a moderate outcome, cases determined to experience serotonin syndrome and/or opioid withdrawal, and cases determined to experience serotonin syndrome and/or opioid withdrawal with at least a moderate outcome. Secondary measures included opioids involved, benzodiazepine treatment, and mechanical ventilation or intubation in cases experiencing serotonin syndrome and/or withdrawal. A potential confounder for this study is concomitant use of any additional serotonergic agents. Additional serotonergic agents reported in the cases will be disclosed in the results. The number of cases determined to meet inclusion criteria will be our study size. We will use descriptive statistics to determine results. Demographic information will include all cases that meet inclusion criteria. As a database review, some cases will be missing data or will be lost to follow up. The primary and secondary outcome results will not include cases that are not followed to medical outcome. Any cases with missing data in the following columns will not be included in the primary or secondary outcome results: symptoms onset after naltrexone HCl/bupropion HCl, opioid involved, naltrexone HCl/bupropion HCl dose.

Results

RADARS identified 33 cases that met inclusion criteria for this study. Demographics for these cases include 28 females (84.9%) and five males

(15.1%) with a mean age of 52.8 and standard deviation of 12.0. The ages range from 26 to 73 years of age. The reported reasons for exposure are as follows: therapeutic error-16 (48.5%), adverse drug reaction-11 (33.3%), intentional misuse-two (6.1%), intentional abuse-two (6.1%), withdrawal-one (3.0%) and intentional unknown-one (3.0%). For all 33 cases, medical outcomes include four major effects, 12 moderate effects, seven minor effects, six not followed due to minimal expected effects, three unable to follow but judged as potentially toxic, and one determined as unrelated effects. Ten cases out of the 33 had missing data and were excluded from any results. Of those cases, none were followed to outcome, and two were lacking data in the symptoms onset field. The demographics of the ten excluded cases are shown in (Table 4). The 23 cases that were followed to medical outcome include four major effects, 12 moderate effects and seven minor effects. Sixteen out of 23 cases (70%) were determined to have at least a moderate outcome. Seventeen cases out of 23 cases (74.0%) were determined to experience serotonin syndrome and/or withdrawal. Overall, 13 out of 17 cases (76.5%) that experienced serotonin syndrome and/or withdrawal were determined to have at least a moderate outcome (Table 5). Thirteen out of 23 cases (56.5%) were administered benzodiazepine therapy. Three out of 23 cases (13.0%) required either mechanical ventilation or intubation. The following opioids were involved in the 17 cases that experienced serotonin syndrome and/or opioid withdrawal: tramadol-six (35.3%), buprenorphine-three (17.7%), hydromorphone-two (11.8%), morphine-two (11.8%), oxymorphone-one (5.9%), hydrocodone-one

(5.9%), oxycodone with fentanyl-one (5.9%) and oxycodone with oxymorphone-one (5.9%). Two cases out of four cases with serotonin syndrome involved tramadol; the remaining two cases involved either buprenorphine or hydromorphone (Table 6). Eight cases out of 23 cases followed to medical outcome reported use of other medications. Duloxetine and cyclobenzaprine, known serotonergic agents, were reported in one case without serotonin syndrome and one case with serotonin syndrome. Out of the six remaining cases that listed other medications, three reported miscellaneous or unknown drugs and three reported drugs without serotonergic activity. If these drugs were taken prior to initiation of symptoms, it is possible they contributed to the interaction.

Table 4

Demographics of the ten excluded cases				
Age	**Sex**	**Reason**	**Opioid**	**Medical Outcome**
62	F	Therapeutic Error	Tramadol	Not followed
>20	F	Therapeutic Error	Oxycodone	Not followed
67	F	Therapeutic Error	Tramadol	Not Followed
26	F	Withdrawal	Methadone	Unable to follow
60	F	Adverse Reaction Drug	Hydrocodone	Not followed
37	F	Adverse Reaction Drug	Buprenorphine	Not followed
52	F	Adverse Reaction Drug	Buprenorphine	Unrelated effect
38	F	Adverse Reaction Drug	Buprenorphine	Unable to follow
56	F	Intentional Misuse	Oxycodone	Not followed
Unknown	F	Therapeutic Error	Methadone	Unable to follow

Table 5

Cases determined to experience serotonin syndrome and/or withdrawal that were followed to medical outcome			
Medical outcome	**Opioid Involved**	**Serotonin Syndrome**	**Opioid Withdrawal**
Major	Buprenorphine	No	Mild
	Hydrocodone	No	Moderate
	Hydromorphone	No	Mild
Moderate	Hydromorphone	Yes	Mild
	Oxymorphone	No	Mild
	Oxycodone/fentanyl	No	Mild
	Tramadol	Yes	Mild
	Morphine	No	Mild
	Buprenorphine	No	Mild
	Tramadol	No	Mild
	Tramadol	No	Mild
	Buprenorphine	Yes	Mild
	Morphine	No	Mild
Minor	Oxycodone/oxymorphone	No	Mild
	Tramadol	No	Mild
	Tramadol	No	Mild
	Tramadol	Yes	Mild

Table 6

Age (yrs)	Sex (M/F)	Opioid involved	Medical outcome	Meets Hunters	COWS
Unknown	M	Oxycodone IR; Oxymorphone ER	Minor effect	No	Mild
33	F	Tramadol	Minor effect	Yes	None
39	F	Methadone	Minor effect	No	None
39	F	Buprenorphine	Moderate effect	No	Mild
40	F	Tramadol	Moderate effect	Yes	Mild
45	F	Tramadol	Minor effect	No	Mild
45	M	Hydrocodone	Major effect	No	Moderate
46	F	Tramadol	Moderate effect	No	Mild
49	F	Buprenorphine	Major effect	No	Mild
51	F	Oxycodone; Fentanyl	Moderate effect	No	Mild
51	F	Morphine	Moderate effect	No	None
52	F	Tramadol	Minor effect	No	Mild
54	F	Morphine	Moderate effect	No	Mild
56	M	Methadone; Hydrocodone IR,	Major effect	No	None
57	M	Tramadol	Minor effect	No	None
59	F	Morphine	Moderate effect	No	None
59	F	Tramadol	Moderate effect	No	Mild
63	F	Hydromorphone	Major effect	Yes	Mild
68	F	Buprenorphine	Moderate effect	Yes	Mild
68	M	Morphine	Moderate effect	No	Mild
69	F	Hydromorphone	Minor effect	No	None
70	F	Hydromorphone	Moderate effect	No	Mild
73	F	Oxymorphone	Moderate effect	No	Mild

Discussion

We hypothesized that patients on chronic opioid therapy would experience a drug interaction with their first dose of naltrexone HCl/bupropion HCl, with at least a moderate outcome. Our study determined 17 out of 23 cases (74%) experienced serotonin syndrome and/or withdrawal. Thirteen cases out of the 17 (76.5%) had at least a moderate medical outcome. Tramadol was the most common opioid involved in patients who experienced serotonin syndrome and/or withdrawal (6/17; 35.5%) and the most common opioid involved in serotonin syndrome cases (2/4; 50%). Some cases may have resulted in a moderate or major outcome without the presence of serotonin syndrome or opioid withdrawal due to the terminology used in the patient's chart limiting the diagnosis. These results support our theory of a potential drug interaction. When naltrexone HCl/bupropion HCl is taken within seven days of an opioid it may indirectly enhance serotonergic activity causing excess stimulation at the 5HT-1A or 5HT-2A receptors through various mechanisms. At least 12 cases of serotonin syndrome reported in the literature involve bupropion; however, these are case reports involving serotonin syndrome. Current literature lacks studies conducted to determine the prevalence of serotonin syndrome given a specific medication or patient population. In alignment with our study, previous studies report tramadol as the most frequent opioid involved in cases of serotonin syndrome.[36] As naltrexone HCl/bupropion HCl is a widely used prescription in the United States, it is important to be aware of the potential risks that are associated. Serotonin

syndrome is not one of the risks mentioned in the package insert as of April 2019.

Study Limitations

The limitations of this study include small sample size, potential for reporting bias, misclassification and confounders. This data represents passive collection of data reported voluntarily from healthcare facilities to poison and drug information centers which ends up in the RADARS post marketing surveillance database. Like other retrospective studies involving the National Poison Data System, collected data may be incomplete and include reporting bias or misclassification. Without complete chart access, it is difficult to diagnose serotonin syndrome or classify opioid withdrawal due to the specific terminology used in Hunter's Criteria and the COWS. It is less likely the terminology in the diagnostic criteria be used in the RADARS database, since it is common for physicians to be unaware of serotonin syndrome. Confounding variables in a retrospective review are likely, with home or ingested medications being our main concern. Without knowing whether the opioids were prescribed or street drugs it is difficult to determine where the focus of awareness and education should lie. This data likely represents an underestimation of cases resulting in serotonin syndrome and/or opioid withdrawal when opioid therapy is not stopped seven to ten days prior to initiation of naltrexone HCl/bupropion HCl.

Future Considerations

Ultimately, this study provides support for further investigation. RADARS database does not contain cases of naltrexone HCl/bupropion HCl without the

use of an opioid. In order to analyze the data further, a control group of patients taking naltrexone HCl/bupropion HCl without opioids may be considered. A database such as Truven or HealthFacts may enhance the study by providing data on how many prescriptions for naltrexone HCl/bupropion HCl are written and their coinciding healthcare visits. RADARS data only includes prescription opioids; however, it does not necessarily tell us whether the ingested opioid was prescribed or not. Accessing a PMP, in order to identify whether the involved opioids were prescribed or street drugs may also benefit in order to evaluate where additional education/counseling to healthcare providers or patients is needed.

Conclusion

Our study suggests patients on opioid therapy may experience a drug interaction in the form of serotonin syndrome and/or opioid withdrawal upon initiation of naltrexone HCl/bupropion HCl. Out of 800,000 prescriptions for this drug, we identified 33 cases that developed adverse effects after their first dose. The true rate of drug interactions is likely higher. Future studies may incorporate healthcare visits associated within a certain timeframe of the filled naltrexone HCl/bupropion HCl prescription along with a control group to compare results.

Appendix A. Clinical Effects/Clinical Notes Terms Used in Text Search

RADARS Search Terms

Clinical effects captured in RADARS that reflect opioid withdrawal include tachycardia, hypertension, abdominal pain, vomiting, nausea, agitated/irritable, excess secretions, diaphoresis, mydriasis, diarrhea, lacrimation, tachypnea, tremor, dehydration, pain (not dermal), rhabdomyolysis, increased CPK.[41]

Clinical effects that are captured in the RADARS notes field that reflect opioid withdrawal searched for via text search for the terms piloerection, withdrawal, and goosebumps, yawning, rhinorrhea, perspiration, restlessness.[41]

Clinical effects captured in RADARS that reflect serotonin excess include tremor, fever, agitated/irritable, tachypnea, hypertension, rigidity, diaphoresis, tachycardia, seizures (single, intermittent or status), renal failure, increased creatinine, disseminated intravascular coagulation, hypotension, nystagmus, mydriasis, excess secretions, confusion, drowsiness/lethargy, coma, hallucinations, ataxia, dystonia, diarrhea, abdominal pain, acidosis, cytopenia, erythema/flushing, rhabdomyolysis, increased CPK.[41]

Clinical effects captured in the RADARS notes field that reflect serotonin excess will be searched for via text search for the terms (serotonin syndrome, clonus, myoclonus, hyperreflexia, increased deep tendon reflex, opisthotonus, increased white blood cell count, leukocytosis, thrombocytopenia, altered mental status, mania, hypomania).[41]

RADARS collects the following reasons for exposure based on AAPCC guidelines: opioid formulation, name and dose, dose of naltrexone HCl/bupropion

HCl, coded duration, major, minor, or moderate death, sex, age, coded acuity, onset of symptoms, generic code for other medications ingested and year.

Appendix B. NPDS Definitions

Medical Outcome

NPDS term	NPDS definition
No effect	The patient did not develop any signs or symptoms as a result of the exposure.
Minor effect	The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucus membranes (e.g. self-limited gastrointestinal symptoms, drowsiness, skin irritation, first-degree dermal burn, sinus tachycardia without hypotension, and transient cough).
Moderate effect	The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement (e.g. corneal abrasion, acid base disturbance, high fever, disorientation, hypotension that is rapidly responsive to treatment, and isolated brief seizures that respond readily to treatment).
Major effect	The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement (e.g. repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation).
Death	The patient died as a result of the exposure or as a direct complication of the exposure.
National Poison Data System.(2016). *NPDS Coding Users' Manual Version 3.2.* American Association of Poison Control Centers	

Appendix B Continued NPDS Definitions

Coding Options Reason for Exposure

Unintentional - Therapeutic error An unintentional deviation from a proper *therapeutic* regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Includes instances in which any type of substance (medications, herbals, non-pharmaceuticals or other products) is substituted for a medication. Drug interactions (or drug/food interactions) resulting from unintentional administration of drugs/foods which are known to interact should also be included.
Unintentional - Unknown An exposure determined to be unintentional but the exact reason is unknown
Intentional - Misuse An exposure resulting from the intentional improper or incorrect use of a substance for reasons **other** than the pursuit of a psychotropic effect.
Intentional - Abuse An exposure resulting from the intentional improper or incorrect use of a substance where the patient was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect.
Intentional - Unknown An exposure that is determined to be intentional but the specific motive is unknown
Adverse Reaction – Drug Unwanted effects due to an allergic, hypersensitivity, or idiosyncratic response to the active ingredient(s), inactive ingredient(s) or excipient of a drug, chemical, or other drug substance when the exposure involves the normal, prescribed, labeled or recommended use of the substance
National Poison Data System.(2016). *NPDS Coding Users' Manual Version 3.2.* American Association of Poison Control Centers

Appendix C. Diagnostic Criteria

Hunter's Criteria

Hunter Serotonin Toxicity Criteria: Decision Rules
In the presence of a serotonergic agent: serotonin toxicity occurs 1. IF spontaneous clonus = yes 2. OR IF inducible clonus = yes AND agitation = yes OR diaphoresis = yes 3. OR IF ocular clonus = yes AND agitation = yes OR diaphoresis = yes 4. OR IF tremor = yes AND hyperreflexia = yes 5. OR IF hypertonia = yes AND temperature > 38˚ C AND ocular clonus = yes OR inducible clonus
Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM.* 2003 Sep;96(9):635-42

Appendix C Continued

Clinical Opioid Withdrawal Scale

Clinical effect	Rating	Score
Resting Pulse Rate	0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	
Sweating	0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	
Restlessness	0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs or arms 5 unable to sit still for more than a few seconds	
Pupil Size	0 pupil pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris visible	
Bone or Joint Aches	0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints or muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	
Runny Nose or Tearing	0 not present 1 nasal stiffness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	
GI Upset	0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting	
Tremor	0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching	
Yawning	0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute	

Anxiety or Irritability	0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult	
Gooseflesh Skin	0 skin smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection	
Total Score	5-12=mild; 13-24=moderate; 25-36=moderately severe; more than 36=severe withdrawal	

Appendix D. Abbreviations or Acronyms

AAPCC: American Association of Poison Control Centers
CDC: Center for Disease Control
COWS: Clinical Opioid Withdrawal Scale
CPK: creatinine phosphokinase
CYP: Cytochrome P450
FDA: Food and Drug Administration
HCl: Hydrochloride
GABA: Gamma-Amino-Butyric Acid
MAOI: Mono Amine Oxidase Inhibitor
NMDA: N-methyl D-Aspartate
NPDS: National Poison Data System
NSAIDS: Nonsteroidal Anti-Inflammatory Drugs
PMP: Prescription Monitoring Program
RADARS: Researched Abused Diversion and Addiction Research System
SNRI: Serotonin Norepinephrine Reuptake Inhibitor
SSRI: Selective Serotonin Reuptake Inhibitor
TCA: Tricyclic Antidepressant

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