Pharmaceutical Misuse

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No Disclosures

Objectives

- Background of Pharmaceutical Abuse
- Some of the more common pharmaceuticals that are abused.
- Four misused medications that we are hearing about more in addiction medicine; Seroquel, Gabapentin, Clonidine, Loperamide
  - What are they and how are they misused.

Pharmaceutical Medication Misuse

- The National Survey on Drug Use and Health (NSDUH)
  - Estimates indicate greater than 16.7 million people 12 and older in the United States abused prescription drugs in 2012,
  - Almost 2.6 million people meeting criteria for a diagnosis of a substance use disorder related to prescription drugs
  - An increase of 250% in prescription drug abuse over the previous 20 years (Substance Abuse and Mental Health Services Administration, 1998, 2013a).
  - During that time, accidental prescription opioid overdoses increased almost 400%, surpassing accidental overdose deaths from heroin, cocaine, and other stimulants combined (Calcaterra, Glanz, & Binswanger, 2013).

Pharmaceutical Medication Misuse

- 2012, prescription drugs were second only to marijuana in prevalence of both illicit use and drug use disorders (SAMHSA, 2013b).
- Opioids are the most commonly abused type of prescription drug and appear to be the largest contributor to these increases.
  - Treatment admissions for substance use disorder services for prescription opioids alone increased 5 to 7 times in various parts of the country from 2000 to 2010 in the U.S. (SAMHSA & Center for Behavioral Health Statistics and Quality, 2014)
  - A self report study of 127 primary care patients receiving opioid medications for treatment of chronic pain revealed that 78% reported one indicator of misuse.
- After opioids, the most commonly abused prescription drugs in the U.S. are tranquilizers (6 million people in 2012) and stimulants (3.3 million) (SAMHSA, 2013).
- Research literature and the media has focused on the abuse of prescription opioids and stimulants, however this problem encompasses the range of psychotropic medications.

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Pharmaceutical Medication Misuse

- 17% of inpatients at a substance use disorder treatment facility had abused antipsychotic medications, such as quetiapine. (Malekshahi, et.al. 2014)
- The prevalence of prescription drug abuse appears to vary based on;
  - the availability of medications with abuse potential, both legal and illegal
  - availability of alternative substances of abuse (Dengenhardt et al., 2008) (Mullins, Rasooly, van den Anker, & Pines, 2014a) (Mazer-Amirshahi, Mullins, Rasooly, van den Anker, & Pines, 2014)
- Individuals with prescription drug abuse are more likely to be;
  - Younger, Single, Caucasian
  - With co-current substance use disorders and/or psychiatric illnesses,
  - Living in rural relative to urban settings (Huang et al., 2006). Tetrault et al., 2008).
- Abusing prescription medication may be perceived as “safer” than abuse of illicit drugs (Fleary, Heffer, & McKyer, 2013; Mateu-Gelabert, Guarino, Jessell, & Teper, 2014).

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Co-Occuring Pharmaceutical Misuse

- Possible explanations as to why medications are misused;
  - mitigate symptoms of substance withdrawal
  - dampen other adverse effects of drugs of abuse,
  - self-medicate co-morbid undiagnosed psychopathology or traits.
- The frequency of misuse in opioid dependent subjects is concerning in that 50% of overdose deaths occur in context to other medications.
  - the majority of opioid overdoses, both fatal and non-fatal, involve multiple central nervous system depressants, most notably alcohol and benzodiazepines.
- There are also high rates of clonidine and gabapentin in opioid overdose victims.

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Pharmaceutical Medication Misuse

The problem is optimizing patient's medical, psychiatric, and addictive disorder treatment while simultaneously avoiding the iatrogenic harm by prescribing medications that may destabilize the patient.

- It is not always clear which medications may be harmful versus beneficial.
  - Benzodiazepines are associated with worse outcomes with buprenorphine:
    - decreased retention in OUD treatment (Fareed et al., 2014; Ferri et al., 2014; Lee et al., 2014);
    - increased risk of emergency room visits (Schuman-Olivier et al., 2013);
    - accidental overdose; death (Häkkinen et al., 2012; Reynaud et al., 1998; Sansone and Sansone, 2015; Seldén et al., 2012).

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Pharmaceutical Medication Misuse

- There are increasing numbers of case reports about the misuse potential of some commonly prescribed medications with psychoactive effects in OUD pts, specifically;
  - clonidine (Seale et al., 2014),
  - gabapentin (Reeves and Ladner, 2014)
  - promethazine (Mendhekar et al., 1999; Zhou et al., 2008) in combination with buprenorphine.
- Psychoactive medication use is common among patients in primary care Office Based Opioid Treatment (OBOT) with buprenorphine.
  - There is evidence gabapentin and clonidine, specifically, appeared to be associated with shorter time to disengagement from buprenorphine treatment. (Weinstein et al. Drug Alcohol Depend. 2018)

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Opioid Use Disorder Patients

- Among patients receiving psychotropics higher dose misuse was reported in rates;
  - 6% clonidine,
  - 36% gabapentin,
  - 50% pregabalin,
  - 29% clonazepam,
  - 27% amphetamine salts.
- Among all patients street use has been reported at;
  - 8% clonidine
  - 11% gabapentin,
  - 5% pregabalin,
  - 19% clonazepam,
  - 8% amphetamine salts.
- In the range of 30% of OUD patients endorsed prescription medication misuse

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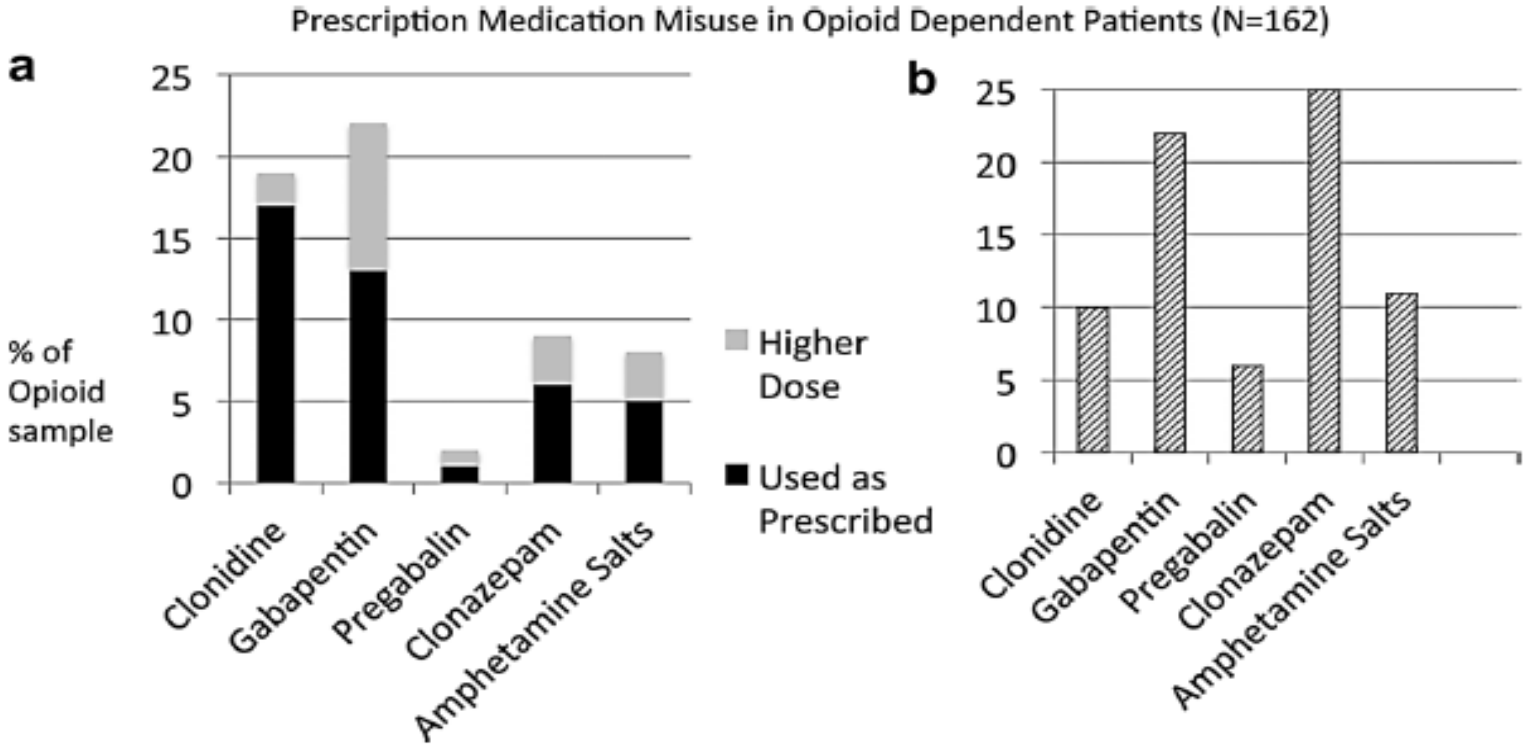
Opioid Use Disorder Patients



a. OUD patients prescribed psychoactive meds, some admitted to misuse
b. OUD patients using unprescribed or misusing prescribed psychoactive meds

Wilens et.al. JAD 2015

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Gabapentin

- Prevalence of gabapentin misuse
  - 1% in the general population
  - 40–65% among individuals with prescriptions,
  - 15–22% within populations of people who abuse opioids.
- Gabapentin recently has been shown useful for mitigating alcohol symptoms as well as anxiety disorders.
- Various subjective experiences have been attributed to the misuse of gabapentin.
  - Similarities to opioids, benzodiazepines, and psychedelics have been reported in a variety of doses.
  - Primarily misused for recreational purposes, self-medication, or intentional self-harm and was misused alone or in combination with other substances, especially opioids, benzodiazepines, and/or alcohol.
    - Individuals with histories of drug abuse were most often involved in its misuse.

Addiction. 2016 July ; 111(7): 1160–1174

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Gabapentin

- FDA approved in 1993 for treatment of epilepsy as an adjunct to anticonvulsant therapy, and in 2004 as an analgesic for post-herpetic neuralgia.
- Gabapentin is an analog of GABA but does not bind to GABA-A or GABA-B
- It can increase GABA and decrease glutamate concentrations
- Its mechanisms of antiepileptic and analgesic actions are unknown,
- It may reduce the release of pain-related peptides and may decrease opioid-induced hyperalgesia
  - gabapentin binding protein has been identified in modulation of neuro-signaling.
- It was been assumed to have no abuse potential.
- Gabapentin is safely tolerated from approximately 800–1800 mg/day
  - The package insert suggest doses as high as 3600 mg/day.
  - In clinical practice, dosing is typically titrated starting from lower doses (i.e., <400 mg/day) and moving rapidly upward.
  - General recommendation is dosing up to 1800 mg in adults. Substantially higher doses have been tested in clinical trials, no additional clinical benefit observed.

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Gabapentin

- Widely used off-label to treat an array of disorders;
  - insomnia,
  - various neuropathic pain conditions,
  - drug and alcohol addiction,
  - anxiety,
  - bipolar disorder,
  - borderline personality disorder,
  - menopausal conditions,
  - vertigo,
  - pruritic disorders,
  - migraines.
- Off-label usage of gabapentin is reported to range from 83–95% which is estimated to account for over 90% of its sales.
  - Due to illegal marketing (promoting off-label uses) of gabapentin, Pfizer was fined $420 million after it was acquired.

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Gabapentin

- Most gabapentin misuse is in individuals with a history of or current substance misuse/abuse/dependence.
  - the majority asso. with opioid misuse
  - Cross-sectional studies of opioid abuse samples in the US and UK estimated gabapentin misuse to be between 15–22%
  - gabapentin abuse with a prescription ranged from 40–65%
  - less evidence of gabapentin abuse among those with a positive history of alcohol abuse or dependence
- Peterson (2009) conducted a study in the US, also utilizing toxicological data, which examined the presence of gabapentin in driving impairment cases.
  - 7% of gabapentin-positive blood samples detected solely gabapentin; the remainder were polysubstance cases, with benzodiazepines (44%), opioids (43%), antidepressants (43%), other CNS depressants (e.g., trazodone, zolpidem; 36%), antiepileptics (25%), cannabinoids (15%), stimulants (11%), and ethanol (6%)
- Smith and colleagues (2012) stated that postmortem toxicology reports in Scotland revealed 75% of those identifying gabapentin also included morphine and/or methadone,
- Several epidemiological studies identify simultaneous combination of gabapentin with other substances for the explicit purpose of misusing them.
  - in combination with buprenorphine for the purpose of “getting high”
  - to potentiate the effects of methadone
- Studies in US and UK substance abuse populations, by Smith (2015) and Smith (2012) respectively, identified a greater likelihood for those misusing gabapentin to also be misusing prescription opioids.
- Smith (2015) also found that individuals who reported using gabapentin to get “high” were also more likely to be misusing benzodiazepines.
- Peterson (2009) benzodiazepines were the most commonly detected class of drugs in combination with gabapentin.

Gabapentin

- A variety of motivations behind gabapentin misuse;
  - substance abuse behaviors in general, which included: recreational use
  - control mood and/or anxiety
  - potentiate the effects of drug abuse treatment
  - intentional self harm
  - Similar to opioids, achieved in combination with other drugs (e.g., buprenorphine/naloxone, methadone, baclofen, quetiapine, alcohol) as well as by using gabapentin alone in dosages ranging from 1500–12000 mg.
- There descriptions of individuals snorting gabapentin powder from capsules and experiencing a high similar to that felt after snorting cocaine
- Commonly reported is the sensation of sedation/relaxation/calmness, with or without other substances (e.g., quetiapine, alcohol, cannabis, buprenorphine/naloxone) over a range of dosages (e.g., 600–4800 mg).
- Other effects experienced included:
  - improved sociability
  - marijuana-like “high
  - cocaine-like “high”
  - “amphetamine rush”
  - disassociation
  - MDMA-like “high”
  - increased energy and focus
  - improved quality of sleep
  - becoming more talkative

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Gabapentin

- Gabapentin requires a prescription, but is not controlled
- Pregabalin, its close structural relative, is Schedule V (abuse potential).
  - It was found that pregabalin had euphoric and sedative properties similar to other frequently abused substances.
- Gabapentin has associated tolerance and physical dependence (with withdrawal symptoms upon discontinuation)
  - these factors may contribute to the escalation or continued misuse of gabapentin in those abusing the drug for its psychoactive effects.
  - There has been consideration of a reevaluation of its abuse potential.
  - It is important to consider in reexamination that gabapentin may be an appropriate treatment for many individuals (e.g., those in alcohol withdrawal, chronic pain, epilepsy)
    - They may face impediments to receiving their medication upon increased control. Therefore, a risk-benefit analysis is necessary prior to any abuse potential labeling.

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Quetiapine (Seroquel)

- Quetiapine is a dibenzodiazepine atypical antipsychotic drug.
  - a potent serotonin 5-HT2a-receptor antagonist and a moderate dopamineD2-receptor antagonist.
    - overall effect is a decrease in dopamine.
    - 5-HT_{2A} and D_2 receptors no significant occupation at doses < 300 mg/day.
  - antagonizes H1, and adrenergic alpha1-2 receptors, no significant activity at cholinergic, muscarinic, or benzodiazepine receptors.
  - At low doses, significant antagonist activity at H1 and alpha1-2 receptors, conferring anxiolytic and sleep-induction, e.g. diphenhydramine.
- Routes of administration in misuse; oral, intranasal, and intravenous
  - Resulting in loss of first pass metabolism and rapid absorption.
- Abuse frequently associated with those who abuse benzodiazepines.
- There are no corroborating animal or human studies to either scientifically confirm or refute the risk of quetiapine misuse/abuse.

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Seroquel Misuse Case Studies

FIRST AUTHOR (COUNTRY, YEAR)	PATIENT DEMOGRAPHICS	DESCRIPTION OF QUETIAPINE ABUSE	OTHER RELEVANT DETAILS
Paparrigopoulos[2] (Greece, 2008)	48-year-old man	1000mg /day orally	Alcohol/benzodiazepine dependence
Murphy[3] (US, 2008)	29-year-old man	Unknown amount, orally	Feigned psychotic symptoms
Reeves[4] (US, 2007)	49-year-old man 23-year-old man 39-year-old man	800mg/day orally 2400mg/day, orally 800mg/day, orally	Alcohol/benzodiazepine abuse Benzodiazepine dependence Exaggerated bipolar symptoms
Pinta[5] (US, 2007)	39-year-old man	600mg/day, orally	Opiate abuse; demanded treatment with quetiapine
Morin[6] (US, 2007)	28-year-old woman	Unknown amount, intranasally	Polysubstance abuse
Waters[7] (US, 2007)	33-year-old man	400–800mg, intravenously	Polysubstance dependence including benzodiazepines
Hussain[8] (Canada, 2005)	34-year-old woman	600 mg, intravenously	Polysubstance abuse, borderline personality disorder

Sansone RA, Sansone LA, Psychiatry (Edgemont) 2010;7(1):13–16

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Quetiapine (Seroquel)

- Reasons for misuse;
  - to “recover” from other substances (66.7%),
  - “enhance” the effects of other substances (25.0%),
  - “experiment” (20.8%).
- The most frequently reported positive effect;
  - “feeling mellow” (75.0%);
- Most frequent negative effects were consistent with antipsychotic use;
  - feeling thirsty,
  - trouble concentrating
- Compared to a normative sample of inpatient substance abusers, ASI composite scores were higher.
- More common among those who also reported misusing prescription sedatives/anxiolytics

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Clonidine

- *Ms*. C was a 28-year-old married woman who abused clonidine in addition to ethchlorvynol, diazepam, methadone, propoxyphene, cocaine, secobarbital, methaqualone, and codeine. She obtained her clonidine from a physician whose office was located near a methadone maintenance program. Her intent was to acquire medication to intensify the effect of methadone and codeine. She was instructed to take the clonidine and to use the diazepam as supportive medication should the withdrawal from opiates become too discomforting. She used one .2-mg clonidine tablet with one or more 10-mg diazepam tablets. She claimed the clonidine made her dizzy and lethargic, and she stopped using it after a couple of weeks in favor of taking just diazepam. Henceforth, she used clonidine only when other drugs were not available or as a means to intensify the euphoric effects of diazepam.

Clonidine

- Reinforcing effects in rats has been identified.
  - no primary physical dependence was not demonstrated. Tierney C. 1988
- Widespread use of clonidine for psychiatric disorders, e.g. childhood hyperactivity, nicotine, alcohol and opiate withdrawal syndromes.
- Reasons for abuse were to ‘boost’ the effects of simultaneously ingested opiates or benzodiazepines, to abate withdrawal symptoms and for its sedative or euphoric properties. Lauzon P,1992; Conway T. Balson A, 1993

Clonidine

- Clonidine hydrochloride, an antihypertensive medication,
- Other symptoms include;
  - sedation, decreased spontaneous motor activity, extension of the sleeping time induced by chloral hydrate, lower body temperature, and mild antipsychotic properties. The most frequent
- Side effects of clonidine include;
  - dry mouth, sedation, dizziness, lethargy, insomnia, hallucinations, depression, and delirium.
  - Most patients have at least one incident of lightheadedness or dizziness upon standing.
- Clonidine has both a central and peripheral action.
- Drowsiness, sedation, and lightheadedness are not reported effects of lofexidine; thus its potential as a drug of abuse is minimal.

Clonidine

https://www.erowid.org/experiences/exp.php?ID=58552

Apps | Open Water Courses | Bank of America — B | Dream Inn - Hotels.c | Content « Substance | The Best Bike Rack, B | 518 Clarice Ave UNIT | Files - Dropbox

Citation: Jeff F.. "Maintenance: An Experience with Clonidine & Methadone (exp58552)". Erowid.org. Aug 28, 2009. erowid.org/exp/58552

DOSE:	1.2 mg	oral	Pharms - Clonidine	**(daily)**
	70 mg	oral	Methadone	**(daily)**

BODY WEIGHT:	230 lb

Some years ago when I was a patient on a methadone maintenance program at a daily dose of 70 mg. of methadone. I used clonidine to potentiate my dose and also as a sedative at night. Clonidine was easy for me to get since I suffered from mild hypertension at the time. My experience was this:

A dose of four 0.3 mg. tabs seemed to about double the effects of my daily 70 mg. dose of methadone and the same dose, for me, was a fast acting and powerful sleep aid. At that dose, however, the side effects were considerable. I would regularly experience positional hypotension (I would pass out sometimes if I stood up quickly) and I had extremely vivid visual hallucinations those times when I would awaken during the night.

Also, after taking clonidine at the dose described above for a couple of months, I ran out of the stuff and thought nothing of it until mid afternoon of the first day when I began to experience classic opioid withdrawal symptomology - even though I had had my usual methadone dose at about 10:AM that day. After a couple of hours feeling the symptoms getting worse and worse, I figured that my discomfort might have something to do with a lack of clonidine and ran to the pharmacy to get a refill. Taking the clonidine again relieved the withdrawal symptoms in about 20 minutes.

Today, I am drug free for the last 20 years and work as a chemical dependency counselor in a behavioral health treatment center where the psychiatrists sometimes use clonidine in off-label ways. One of them told me that he has prescribed cloindine (I don't know at what dose) for nightmares associated with PTSD. I think it is also sometimes used to treat the symptoms of Obsessive Compulsive Disorder in some patients.

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Loperamide

- This 26-year-old Caucasian female presents with a history of having started using opioid pain medications in 2011. She had a couple of short periods of abstinence, however 4 and 1/2 years ago she started buying them on the street and using consistently. Two years ago she started using loperamide and over the last year has been using 400 mg a day. Patient had experienced a couple of episodes of lightheadedness and near fainting spells without exertion or change in position. On July 4 of this year she had a cardiac arrest. On being hospitalized it was determined that she had a cardiac arrhythmia secondary to prolonged QT interval. Her initial QT interval was 647msec. Patient had difficult time in the hospital initially because it was not determined that she was in opioid withdrawal and she became very agitated. Following an evaluation by the addiction medicine consult service she was initiated on buprenorphine. Patient responded to this medication well and has been maintained on the medication since that time. She believes that her primary reason for continuing to use loperamide was to stay off withdrawal.

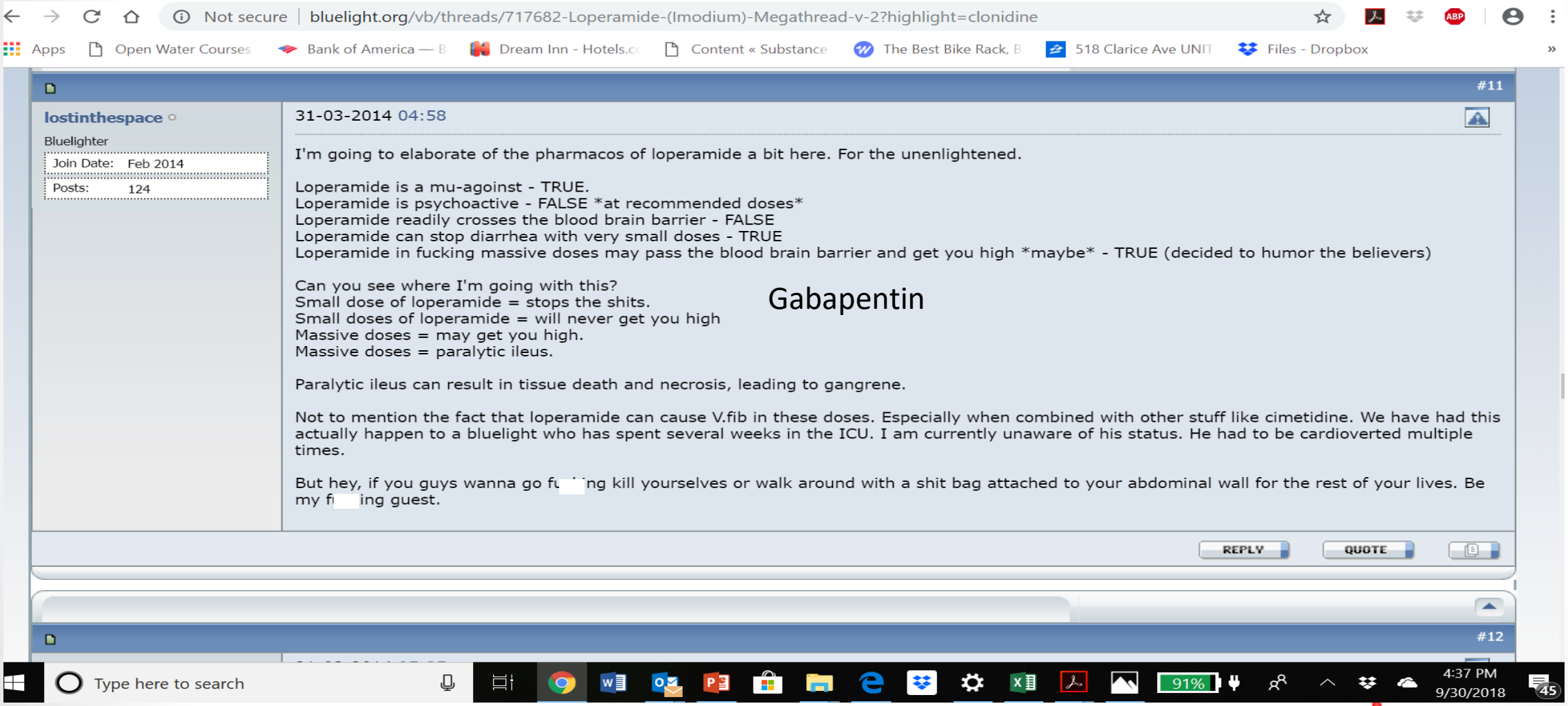
Loperamide

- Loperamide, a phenylpiperidine derivative FDA approved in 1976 has an antidiarrheal agent and classified as a Schedule V Controlled Substance.
  - Sold over-the-counter (OTC) formulation starting in 1988.
  - At therapeutic doses, loperamide stimulates the mu-opioid receptor in the myenteric plexus.
  - It has low central nervous system (CNS) bioavailability due to CNS efflux by P-glycoprotein.
  - However when administered with a P-glycoprotein inhibitor, or taken at high doses, it becomes bioavailable as an opioid agonist in the CNS. (Bhatti et al., 2017).
- Loperamide non-medical use has been documented (Leo et al., 2017)
- Its use as an opioid substitute is increasing (Bhatti et al., 2017).

Loperamide

- The FDA has issued statements with safety concerns associated with loperamide.
  - The FDA warned of serious cardiac problems that can occur with non-medical use of loperamide.
  - There was a report of 48 cases of loperamide misuse at high doses.
  - 31 of these cases resulted in hospitalization and 10 patients died.
- Loperamide in doses 40 to 100 times the therapeutic dose can result in QTc prolongation and torsades de pointes (Leo et al., 2017).

Loperimide



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Some Resources

- www.pcssnow.org
  - Provider clinical support system for medication assisted treatments
- www.aoaam.org
  - Amer. Osteo. Acad. of Addiction Medicine
- www.asam.org
  - Amer. Soc. Of Addiction Medicine
- www.drugabuse.gov/ NIDA
- www.NIAAA.nih.gov/ NIAAA
- www.naabt.orgBuprenorphine advocate siteor
- www.buprenorphine.samhsa.gov/rovider locator