HHS Public Access

Author manuscript

Addict Behav. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Addict Behav. 2017 July ; 70: 61–64. doi:10.1016/j.addbeh.2017.02.008.

Identification of non-steroidal anti-inflammatory drug use disorder: A case report

Corresponding author: Alicia S. Ventura, MPH, Boston Medical Center, 801 Massachusetts Avenue, 2nd Floor, Boston, MA 02118, Phone: (617) 414-6914, Fax: (617) 638-4483, Alicia.ventura@bmc.org.

Role of Funding Sources

Funding for this study was provided through a cooperative agreement with the National Institute on Alcohol Abuse and Alcoholism (NIAAA); grant number: U01AA020784. NIAAA had no role in the conception of this case report, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

Contributors

RS was principal investigator of the study and obtained funding to support all research operations. ASV was the project manager and oversaw data collection. AYW conceived of the case report. MEG and LKV conducted literature reviews. AYW performed a detailed review of the participant's medical record. MEG completed the initial draft of the manuscript; LKV assisted. ASV, AYW and RS provided considerable editing, revisions and content review of initial draft and all authors read and approved the final draft of the manuscript.

Conflict of Interest

Dr. Alexander Walley is employed as a general internist and addiction specialist at Boston Medical Center and Boston University School of Medicine. His salary is supported in part by the Massachusetts Department of Public Health, where he serves as the medical director of the opioid overdose prevention pilot program. He also receives salary support through his work on research, education, and program grants which have been funded since 2007 by the National Institutes of Health, Substance Abuse Mental Health Services Administration, Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, the Massachusetts Department of Public Health and the Burroughs Welcome Trust. The topics of these grants have included overdose prevention and rescue interventions, integration of addiction treatment and medical care, education and training of addiction researchers and providers, the improvement of care models for people with HIV and substance use. He has been paid to speak or had travel reimbursed to speak or to consult for numerous professional and scientific organizations, all non-profit or governmental organizations, since 2007, such as the American Society of Addiction Medicine (ASAM), the University of British Columbia Center for Excellence, the Boston University Continuing Medical Education Safe and Competent Opioid Prescribing Education Course and the Prescribe to Prevent Overdose Prevention Course, New England AIDS Education and Treatment Center, the Food and Drug Administration, and the Open Society Institute. He is an unpaid board member of AMERSA, the Addiction Medicine Fellowship Director's Association and the East Chop Tennis Club, all non-profit organizations. He holds no stock investments in businesses that overlap with the topic of his work, such as pharmaceutical, addiction treatment or alcohol beverage companies.

Dr. Richard Saitz is and has been principal investigator of grants awarded to Boston Medical Center and Boston University from the National Institutes of Health (including NIAAA and NIDA, and the Substance Abuse and Mental Health Services Administration) to study the management of unhealthy substance use, including to test the accuracy of screening and the efficacy of screening, brief intervention and referral to treatment and the effectiveness of integrated care. He has been paid to speak or had travel reimbursed to speak or to consult for/at numerous professional and scientific organizations, all non-profit organizations for over a decade, such as the American Society of Addiction Medicine (ASAM), RAND, the Research Society on Alcoholism, The BMJ, the Institute for Research and Training in the Addictions, the International Conference on Treatment of Addictive Behaviors, and the International Network on Brief Intervention for Alcohol and other drugs (INEBRIA), and numerous universities and hospitals. He is an author and editor for Springer, UpToDate, the American Society of Addiction Medicine, the BMJ and the Massachusetts Medical Society (royalties and/or honoraria). Wolters Kluwer has supported conference travel to an editors[1] meeting. Systembolaget, a Swedish government agency that aims to minimize alcohol-related problems, supported transportation and lodging for a presentation on brief intervention at an INEBRIA thematic meeting in 2016. Alkermes provided medication for an NIH-funded trial of alcohol disorder treatment effectiveness. He has been paid to serve as an expert witness in malpractice cases related to the management of alcohol and other drug disorders. In 2009 he consulted for Inflexxion and Medical Directions, in 2008 and 2004 for Saatchi and Saatchi healthcare, in 2006 for Fusion Medical Education, in 2004 for the Lewin Group, in 2002 for Axis-Shield ASA and Forest Pharmaceuticals. Has has also consulted regarding research for Yale University, Brandeis University, Group Health Inc, Beth Israel-Deaconess Hospital, and other universities. He spoke at a National Press Foundation event on the terminology of addiction and received no compensation but the meeting was funded by ASAM, Open Society Foundations, Pew Charitable Trusts, Shatterproof, Hazelden Betty Ford Foundation and the Addiction Technology Transfer Center Network. He is employed by Boston University School of Public Health.

All other authors declare that they have no conflicts of interest.

Margo E. Godersky, MPH[a], **Laura K. Vercammen, MPH**[a], **Alicia S. Ventura, MPH**[a,b], **Alexander Y. Walley, MD, MSc**[b], and **Richard Saitz, MD, MPH**[a,b]

[a]Department of Community Health Sciences, Boston University School of Public Health, 801 Massachusetts Ave, 4th Floor, Boston, MA, USA

[b]Clinical Addiction Research and Education Unit, Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine and Boston Medical Center, 801 Massachusetts Ave, 2nd Floor, Boston, MA, USA

Abstract

Commonly used for analgesic and anti-inflammatory effects, non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medications in the world. In spite of their prevalence, reports of NSAID misuse and NSAID use disorder are uncommon. This case report describes a research participant who met criteria for DSM-5 moderate substance use disorder based on her use of prescribed ibuprofen as assessed by the validated Mini International Neuropsychiatric Interview (MINI). This case demonstrates that the DSM-5 criteria within the MINI can be applied to diagnose an NSAID use disorder. Addiction researchers and clinicians should consider medications generally not thought to be addictive, like NSAIDs, when evaluating patients for substance use disorder.

Keywords

NSAID; substance use disorder; dependence; case report; diagnosis

1. Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications in the United States, accounting for 60% of over-the-counter (OTC) analgesic sales and over 100 million prescriptions each year (Conaghan, 2012). In 2010, approximately 72 million people in the US used an NSAID three or more times a week for at least three consecutive months (Zhou et al., 2014). Studies designed specifically to measure patterns of NSAID use found that knowledge of adverse side effects was low, OTC and prescription NSAIDs were inappropriately used together and the use of quantities higher than recommended was common (Wilcox et al., 2005). Patterns of NSAID use have been associated with risk of adverse medical consequences such as acute interstitial nephritis and upper gastrointestinal bleeding (Castellsague et al., 2012).

Despite widespread prevalence of NSAID use at the population level and frequent use above recommended doses, there are few reported cases (Etcheverrigaray et al., 2014; Jiang and Chang, 1999) of NSAID use disorder in the literature or national survey data. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes specific mention of NSAID use disorder in the “other (or unknown) substance use disorders” subcategory, along with drugs such as anabolic steroids and antihistamines (American Psychiatric Association, 2013). A 2003 survey of 36,309 non-institutionalized people over 18 found that only 0.04% of those surveyed met criteria for DSM-5 substance use disorder

under the subcategory of “other drug use” (NIAAA, 2003). Similarly, the 2012 National Survey on Drug Use and Health found that of 68,309 individuals surveyed, only 0.3% (n=190) reported ever using a NSAID “non-medically,” the majority of whom were specifically using ibuprofen (Substance Abuse and Mental Health Services Administration, 2013).

To our knowledge, only one case report exists in the literature describing DSM-5 NSAID use disorder (Etcheverrigaray et al., 2014). That particular case report focuses primarily on hypothesized physiological mechanisms for NSAID dependence and describes a 17-year old female patient with depression who consumed increasingly high doses of prescribed ibuprofen initiated for knee pain; she met eight of eleven DSM-5 substance use disorder criteria as assessed by her psychiatrist as well as an addiction specialist. Other notable mental health-related case reports related to NSAID use describe patients with psychiatric disorders resulting in mania or psychosis that were exacerbated by NSAID use (Jiang and Chang, 1999).

Herein we describe a case of a participant enrolled in an observational cohort study of adults living with HIV and current substance dependence (DSM-IV criteria, past 12 months) or ever injection drug use. The case participant was eligible for the cohort study only because she met criteria for NSAID use disorder, which were the only substance use disorder criteria she met. This was the only case of NSAID use disorder identified among 673 patients screened for study eligibility.

2. Case description

The participant was a 58-year-old, Black female of Haitian descent, living with HIV. She was screened in 2014 by research staff, trained by addiction medicine certified and HIV care specialist physicians and researchers and a Masters level trained project manager, in order to assess eligibility for a cohort study in an HIV primary care clinic within an urban academic medical center. Upon screening, the participant met criteria for both DSM-IV NSAID dependence, as well as criteria for DSM-5 moderate NSAID use disorder based on an assessment using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The MINI has been validated in both research and non-research settings against established diagnostic instruments such as the Composite International Diagnostic Interview (CIDI) and the Structured Clinical Interview for DSM-III-R Patients (SCID-P) (Sheehan et al., 1998). In response to the initial MINI prompt, used to assess past-year drug use, the participant reported using an NSAID more than once in the past 12 months “to get high, to feel elated, to get a ‘buzz,’ or to change her mood” (Sheehan et al., 1998). The participant’s responses to questions designed to assess each specific DSM-IV and DSM-5 substance use disorder criterion are detailed in Table 1. In total, she met 4 out of 11 substance use disorder criteria related to her use of ibuprofen, which met the threshold for DSM-5 moderate substance use disorder (American Psychiatric Association, 2013). The participant denied using any drug non-medically other than ibuprofen in the previous 12 months. She did not meet criteria for an alcohol use disorder and denied any injection drug use. Written informed consent was obtained from all study participants and study procedures were approved by the

Boston Medical Center Institutional Review Board. Additional specific written informed consent was obtained from the participant for publication of this case report.

At study entry, past 30-day illicit drug use (both prescription and non-prescription) was assessed using the Addiction Severity Index (Zanis et al., 1994). The participant reported no illicit or nonmedical drug use in the past 30 days, with the exception of ibuprofen, which she was prescribed for pain by her physician and reported taking in amounts greater than prescribed. At that time, the participant disclosed that she was also prescribed gabapentin and cyclobenzaprine for pain and was taking both medications as prescribed by her physician. A review of her electronic medical record confirmed current prescriptions for ibuprofen, gabapentin, and cyclobenzaprine. All 3 of these medications had been documented on the patient's medication list since at least 2012. No other pain medications (e.g. opioids or other analgesics), or medications known to have addictive potential, were identified in the medical record. The prescription for ibuprofen was to take 600mg by mouth every six hours as needed.

The participant's medical record review also revealed pain conditions, including fibromyalgia diagnosed by a rheumatologist in 2010 and peripheral neuropathy diagnosed by a neurologist in 2011. In contrast to her answers during the research assessment, there was no indication in the medical record that she had been taking more ibuprofen than prescribed, with the exception of one note by her primary care physician reporting new mouth and throat pain. In June 2014 it was documented: "Foods that she usually eats sometimes causes [sic] burning in her throat; her headache never goes away. Sometimes she doubles up her Motrin (ibuprofen) dose but this doesn't help. She confirms she is also taking Neurontin (gabapentin) and Flexeril (cyclobenzaprine) for her pain. In the morning when she awakens she sometimes cannot speak because the pain is so severe; she becomes tearful when describing it. She reports that it takes her 'forever to eat and swallow and chew because of her mouth pain." This pain was further investigated at appointments with otolaryngology and dental specialists and then upper endoscopy in March 2016, which was notable for gastritis and duodenitis. Other than these findings on endoscopy, no medical complications from ibuprofen were apparent on medical record review. It is not known if she was aware of the findings and their likely connection to ibuprofen use.

At study entry, the participant had viral suppression (HIV viral load less than 50 copies/mL) and had a high CD4 cell count (920/mm^3), indicative of well-controlled HIV infection. The participant's medical record showed a diagnosis of major depressive disorder, which was consistent with her responses to the Patient Health Questionnaire-2 (PHQ-2), a validated screening tool for depression (Gilbody et al., 2007) that was administered at study entry. She also met criteria for an anxiety disorder measured by the Overall Anxiety Severity and Impairment Scale (OASIS), a validated instrument also administered at study entry (Campbell-Sills et al., 2009).

Recent alcohol use was assessed at study entry by 30-day Timeline Followback (Sobell & Sobell, 1992); the participant reported drinking one standard drink (14g ethanol) on one day in the past 30 days. At this same study visit a dried blood spot was collected from the participant and tested for phosphatidylethanol (PEth), a marker of recent heavy alcohol use,

to confirm self-reported measures of recent alcohol use (Stewart et al., 2014). The participant's PEth result was negative (less than 8 ng/mL), indicating no recent heavy drinking, which was consistent with her self-reported past 30-day alcohol use (i.e. of one standard drink). At a separate visit, the participant completed a detailed interview-based assessment of lifetime drug use; she denied any illicit drug use in her lifetime (McLellan et al., 1980).

At study entry, the participant disclosed that, in the past three months, she had taken prescription drugs (specifically ibuprofen) in greater amounts than prescribed to treat her pain or discomfort. She also reported chronic pain for the past 20 years "all over or mostly all over [her] body." The Brief Pain Inventory, an instrument that assesses both intensity of pain and interference of pain in one's life, was administered (Cleeland, 1991). On a standard 10-point pain scale, with 0 representing no pain and 10 representing "pain as bad as you can imagine," the participant reported that in the past week, on average, her pain was a 6; she rated her worst pain in the past week a 7. By comparison, the average pain score among all 250 participants enrolled in the study was 5.3. With regard to interference of pain with her daily activities-including general activity, walking ability, work/housework, mood, enjoyment of life, relations with others, and sleep- the participant reported an overall pain interference rating of 5.8. The daily activity her pain most interfered with was sleep (rated 7 on 10-point pain scale). The level of pain interference reported by the participant was comparable to the level reported by other cohort participants.

At the follow-up assessments, she reported that she had stopped taking ibuprofen and no longer met criteria for a prescription medication use disorder.

3. Discussion

NSAID use disorder is uncommon. Accordingly, the purpose of this report is to describe a case of a 58-year old woman with ibuprofen misuse (taking more than prescribed) and DSM-5 moderate NSAID use disorder. She reported no other non-medical use of prescription medications or illicit substance use in her lifetime and denied any misuse of other medications prescribed to treat pain–including opioids and gabapentin, which are recognized as substances with higher potential for misuse than NSAIDs (Schifano, 2014). NSAIDs, generally thought to have little or no addictive potential, are not classified as a controlled substance; in fact, they have been used as a replacement for placebo in pain-related clinical trials (Adams et al., 2006).

Though documented in national epidemiologic studies of substance use, the prevalence of NSAID use disorder is low and few detailed descriptions of such cases (perhaps only one) appear in the peer-reviewed literature. In contrast to the only other case report of NSAID use disorder we identified, the case reported herein met fewer DSM-5 substance use disorder criteria, was older, had chronic pain and was identified within a research context. In the presented case, despite multiple prescriptions and physicians addressing the patient's chronic pain, there was no documented concern from her medical providers regarding NSAID misuse.

This case raises important questions about optimal clinical and research approaches to uncommonly reported and identified substance use disorders. In this case, NSAID use disorder was identified during a research assessment but was not identified during routine clinical care. NSAID use disorders may be under-identified (or under-reported) substance use disorders that could warrant intervention and treatment. Although there was no evidence in the present case of physical symptoms or consequences of NSAID use, other than gastrointestinal inflammation of which she and her clinicians were not aware until after she met disorder criteria, the participant reported negative consequences of her ibuprofen use, specifically craving, tolerance and impaired control. One might believe that NSAID use disorder would be inconsequential yet these consequences signal the need for attention to the substance, its use and an evaluation of clinically significant impairment or distress. In an analysis within this cohort, the number of substance dependence criteria, *not* type of substance used, was shown to be associated with negative health consequences, such as a lack of HIV virologic control (Nolan et al., 2015).

This case illuminates potential tension that can occur when applying diagnostic criteria strictly in a research setting. Clinicians might discount the criteria met by the participant in our reported case as reflective of uncontrolled pain and the participant's desire to relieve it—akin to pseudo-addiction (Weissman and Haddox, 1989), a controversial concept that has not been consistently established in the literature (Greene and Chambers, 2015). However, the participant endorsed four DSM-5 criteria (i.e., tolerance, using more than intended, failure to stop and craving) and thus exceeded the diagnostic threshold for substance use disorder on a validated measure administered by a trained researcher. The DSM-5 criteria for tolerance and withdrawal as a consequence of a prescribed medication do not (alone) suffice for a diagnosis of prescription drug use disorder; however, this patient met three criteria other than tolerance and withdrawal.

This case echoes the diagnostic challenges associated with substance use disorders for other pain medications that are more commonly considered re-enforcing. Had the medication in question been an opioid, we suspect most clinicians and researchers would agree the patient met criteria for a substance use disorder. As ibuprofen is not commonly identified as the main substance used in substance use disorders, it is reasonable to question whether the symptoms detected during the study assessment were directly caused by brain changes from using ibuprofen or whether these symptoms were motivated primarily by relieving her underlying pain. In this case, the participant answered the diagnostic question of using ibuprofen "to get high, to feel elated, to get a 'buzz,' or to change her mood," thus reporting a psychoactive experience from using the substance. Furthermore, the ibuprofen use and the symptoms of substance use disorder were reported as occurring during the same time period. Later, both the ibuprofen use and the symptoms were reported by the participant to be resolved at follow-up assessments. We do not have further data to support nor disprove a causal relationship.

While NSAIDs are generally viewed as safer alternatives to opioids or other analgesics, without potential for addiction, these medications can have negative consequences and, in rare cases, can be part of a substance use disorder. Given the extensive use of medications like NSAIDs in the general population, and the low perceived risk for addiction associated

with their use, we encourage the use of the DSM-5 criteria to diagnose substance use disorders for all prescription medications, including NSAIDs such as ibuprofen. Study of the clinical course of the subgroup of individuals with non-opioid prescription drug use disorders is warranted. Additional research is needed to understand prognosis and the role for clinical interventions, such as psychotherapy or medication monitoring.

Acknowledgments

Funding for this study was provided through a cooperative agreement with the National Institute on Alcohol Abuse and Alcoholism (NIAAA); grant number: U01AA020784. The authors would like to thank all of the Boston ARCH Cohort study participants for the time and effort they have dedicated to this research. We also wish to thank all staff at Boston University and Boston Medical Center who supported this project. Specifically, we want to acknowledge Kate Haworth and Keshia Toussaint for their efforts collecting participant-level data for this case report.

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Highlights

- We identified a case of non-steroidal anti-inflammatory drug (NSAID) use disorder in a patient with no other substance use disorder.
- NSAIDs are commonly used but rarely reported as drugs with addiction potential.
- Recognition of substance use disorders in a research setting may differ from clinical assessment.

Table 1

Substance Use Disorder (SUD) Criteria Assessed at Study Entry (DSM-IV & DSM-5) by MINI 6.0

Modified MINI Questions (Version 6.0)	Corresponding SUD Criterion	Criterion Met?
1. Have you been intoxicated or hungover from *ibuprofen*, when you had responsibilities at school, work or home? Did this cause you problems?	Social Impairment	No
2. Have you been intoxicated from *ibuprofen* in any situation where you were at-risk of physical injury (e.g. driving a car, using machinery)?	Risky Use	No
3. Did you ever have legal problems because of your *ibuprofen* use? (*DSM-IV criterion only)*	Legal	No
4. If *ibuprofen* caused you problems with your family or friends, did you continue to keep using it?	Social Impairment	No
5. Have you needed to use much more *ibuprofen* to get the same effect as when you first started taking it?	**Tolerance**	**Yes**
6. When you reduced or stopped using *ibuprofen*, did you have withdrawal symptoms? Did you use any other drug to keep from getting sick or to feel better?	Withdrawal	No
7. When you used *ibuprofen* did you end up taking more than you thought you would?	**Impaired Control**	**Yes**
8. Have you tried to stop taking *ibuprofen* but failed?	**Impaired Control**	**Yes**
9. On the days that you used *ibuprofen* did you spend a lot of time using, obtaining, thinking about, or recovering from *ibuprofen*?	Impaired Control	No
10. Did you spend less time working, on hobbies, or with your family or friends because of your *ibuprofen* use?	Social Impairment	No
11. Did you continue to use *ibuprofen* even if it caused you problems with your health?	Risky Use	No
12. Did you feel a very strong desire or urge to use *ibuprofen*? (*DSM-5 criterion only)*	**Craving**	**Yes**

Abbreviations: SUD, substance use disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5th edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; MINI 6.0, Mini International Neuropsychiatric Interview version 6.0.