Heliyon 10 (2024) e26111

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Case report

Severe cerebral edema related to oral methadone: A case report and literature review

Carlos A. Cañas [a,b,*], Ivan Posso-Osorio [b,c], Robert Rivera-Londoño [d], Juan D. Bolaños [d], Ana M. Granados [e]

[a] Universidad Icesi, CIRAT: Research Center in Rheumatology, Autoimmunity and Translational Medicine, Valle del Cauca, Cali, Colombia
[b] Fundación Valle del Lili, Rheumatology Unit, Valle del Cauca, Cra. 98 No. 18-49, Cali, 760032, Colombia
[c] Universidad Icesi, Faculty of Health Sciences, Valle del Cauca, Cali, Colombia
[d] Fundación Valle del Lili, Clinical Research Center, Cali, 760032, Colombia
[e] Fundación Valle del Lili, Radiology Unit, Valle del Cauca, Cra. 98 No. 18-49, Cali, 760032, Colombia

ARTICLE INFO

Keywords:
Toxic leukoencephalopathy
Opioids
Oxycodone
Opioid withdrawal
Withdrawal syndrome

ABSTRACT

Introduction: Opioids are widely used for pain management, and increased intracranial pressure (ICP) has been evidenced in some cases. We reported a patient with severe cerebral edema after initiating methadone and its complete resolution upon discontinuing the medication. Additionally, a review of the literature is made.

Case report: A 53-year-old woman patient with a history of systemic lupus erythematosus developed mechanic chronic lower back pain, refractory to conventional treatments. She presented improvement with oxycodone. She withdrew this medication due to a lack of supplies in her country (Colombia) and showed withdrawal symptoms. She consulted the emergency department, where oral methadone was started and symptom control was achieved. Three days after admission, she presented intense headaches and emesis. A brain CT scan was performed in which severe cerebral edema was appreciated. Methadone was discontinued, and neurological symptoms quickly disappeared. A follow-up brain CT scan was performed later, finding full resolution of the edema.

Conclusion: A case of severe cerebral edema associated with the initiation of oral methadone and its rapid resolution without neurological sequelae after its withdrawal is presented, clinicians must be attentive to this adverse event.

1. Introduction

The effects of opioids on intracranial pressure (ICP) have been controversial for a long time [1]. Opioids are generally considered safe, and their use, mainly morphine and fentanyl's, has been accepted for several decades for neurosurgical patients [2]. However, isolated cases of increased ICP have been reported with fentanyl [3], morphine [4], sufentanil [5], codeine [6], alfentanil [], and heroin [7], among others [8]. Clinicians are even cautioned to consider opioids a contributing factor in refractory intracranial hypertension [9].

* Corresponding author. Universidad Icesi, CIRAT: Research Center in Rheumatology, Autoimmunity and Translational Medicine, Valle del Cauca, Cali, Colombia.
E-mail address: cacanas@icesi.edu.co (C.A. Cañas).

https://doi.org/10.1016/j.heliyon.2024.e26111
Received 14 August 2023; Received in revised form 13 January 2024; Accepted 7 February 2024
Available online 13 February 2024
2405-8440/Â© 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The cause of opioids-associated increase in ICP is unknown. Both morphine and fentanyl can increase ICP and concomitantly decrease both mean arterial pressure and cerebral perfusion pressure without a significant effect on the difference in arteriovenous oxygen content or mean middle cerebral artery flow velocity [10], which suggests that other mechanisms, in addition to the activation of the vasodilator cascade, are involved.

Otherwise, in recent years there have been several studies and case reports that describe a probably new clinical condition related to opioid use known as opioid-induced toxic leukoencephalopathy. This condition is characterized by a diverse range of neurobehavioral symptoms, including altered mental status, psychomotor changes, seizures, and even coma, typically with spared language capabilities. While these symptoms may not readily indicate an underlying cause, they have become a subject of growing interest and concern within the medical community due to their association with opioid use [11–13]. Opioid-induced toxic leukoencephalopathy is relevant as it falls within the spectrum of potential neurological complications associated with opioid medications.

Opioids, including commonly used medications like morphine and fentanyl, have been deemed safe for the management of pain, even for neurosurgical patients. Nevertheless, the medical community has noted sporadic cases of increased ICP associated with various opioids, sparking concerns about their potential implications. In recent years, there has been growing interest in understanding the intricate relationship between opioid use and neurological complications. The rationale for this study stems from the increasing recognition of adverse events related to opioid medications, such as methadone, and the need to shed light on atypical presentations. Amid, and as a contribution to, this evolving landscape, we present a compelling case report of a patient who experienced severe cerebral edema linked to oral methadone usage that fell within these spectra. Additionally, an unstructured literature review of cases of neurotoxicity associated with methadone use was made.

2. Case presentation

A 53-year-old woman from Cali, Colombia, was admitted for symptoms of oxycodone withdrawal four days earlier (anxiety, irritability, restlessness, and generalized muscle aches). The reason for the withdrawal was not voluntary and was due to the lack of availability of the drug in Colombia.

The patient had a history of systemic lupus erythematosus (SLE), which began when she was 28 years old, with joint, mucocutaneous, hematological (cytopenia), hepatic and renal involvement (type III lupus nephritis), in addition to the presence of antinuclear antibodies (ANAs) and positive anti-dsDNA in high titers and complement consumption. She received oral corticosteroids, intravenous cyclophosphamide for six months, and then azathioprine for 18 months. Corticosteroids were gradually tapered and then withdrawn. The patient was in complete remission until now. Six years earlier, she had started experiencing low back pain associated with multiple episodes of lumbar disc disease, refractory to conventional treatments, including physical therapy, infiltrations, and different analgesics. For this reason, for the past six years, she had been taking 20 mg of oxycodone tablets three times a day without interruption.

Upon physical examination, the patient's vital signs were: blood pressure 110/72 mmHg, pulse rate 74 beats/min, temperature 36.7 °C, O_2 saturation 94%, at FiO_2 21%. The head and neck were normal. There were no abnormal findings on the cardiopulmonary or abdominal examination. The skin was normal. No joint inflammatory signs were found. The neurological examination was regular, fundus ophthalmological examination was normal. Laboratories were normal, including liver and kidney function tests. Antinuclear

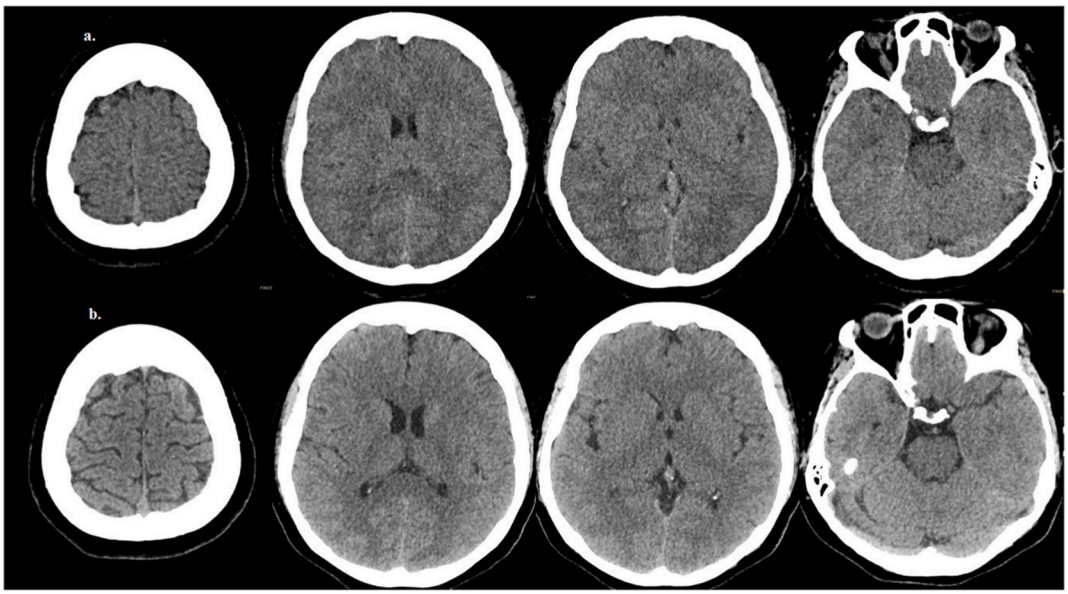

Fig. 1a. Initial non-enhanced cranial CT with generalized effacement of cerebral sulci and cerebellar folia, diminished ventricular spaces, and no evidence of herniation. Fig. 1b: Follow-up CT evidencing complete resolution of the cerebral edema.

antibodies and anti-DNA antibodies were negative. Complement C3 and C4 levels were normal.

The patient was admitted, and 500 mg of intravenous paracetamol every 6 hours and 10 mg of oral methadone every 8 hours were started. Improvement in symptoms related to opioid withdrawal with reasonable pain control was observed.

Three days after admission, the patient began to complain of intense headache, blurred vision, and intractable vomiting, adding a generalized tonic-clonic seizure that lasted approximately 4 min with postictal drowsiness for several hours.

Upon the onset of these new symptoms, a comprehensive diagnostic workup was initiated. Brain CT scans were performed using a multidetector scanner with a slice thickness of 5 mm, enabling visualization of severe cerebral edema characterized by brain sulcal effacement and diminished ventricular space, with no apparent intracranial cause (Fig. 1a). She was transferred to the intensive care unit; methadone was suspended, and 8 mg of intravenous dexamethasone every 8 hours for two days were started. Neurological symptoms quickly disappeared. A follow-up brain CT scan was performed 72 hours after the initial scan, finding retrieval of the ventricles and brain sulci (Fig. 1b). Additionally, a contrasted cerebral magnetic resonance imaging (MRI) was performed using a 1.5 T scanner. The MRI protocol involved T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and contrast-enhanced T1-weighted sequences. This MRI evaluation served to rule out any structural brain damage and provide a more detailed assessment of the patient's neurological condition. These diagnostic procedures were conducted under standard radiological protocols, and the images were interpreted by experienced neuroradiologists, ensuring the accuracy and reliability of the findings. (Fig. 2).

Laboratory tests performed during the neurological episode were normal (Hb: 15.1 gr/L, white blood cell count: 6810/mm3, neutrophils: 3960/mm3, lymphocytes: 1920/mm3, monocytes: 600/mm3, platelets: 328,000/mm3, BUN: 19 mg/dL and creatinine: 0.7 mg/dL, AST: 22 UI/mL, ALT: 29 UI/mL, TSH: 1.41 mIU/L, FT4: 1.23 ng/dL, calcium: 9.56 mg/dL, phosphorus: 3.67 mg/dL, vitamin B12: 723 ng/mL, C3: 125.39 mg/dL, C4: 19.24 mg/dL and low anti-dsDNA levels). Also, a complete evaluation for thyroid disorders, HIV, hepatitis, and other infectious and metabolic sources was negative.

The patient was prescribed 20 mcg/hour of buprenorphine patches with good tolerance and therapeutic response. At discharge, ten days after admission, she was asymptomatic.

3. Discussion

We present the case of a patient with chronic low back pain and a long history of opioid use, who consulted because of withdrawal-related symptoms managed with methadone, and who later developed acute cerebral edema [14]. Although our patient did not present the classical manifestations and typical patterns of opioid-related toxic leukoencephalopathy associated with methadone use, such as hyperintensities of the brain white matter with diffusion restriction [15], there have been other reports of opioid intoxication that manifested with brain edema like this case [11,13,16–19].

The strengths of this case are based on the observation of how, after taking a medication such as oral methadone, a clinical picture of cerebral edema is triggered. When the drug is withdrawn, an improvement occurs. All of the above make it a probable adverse drug reaction according to Naranjo's scale ($\geq$5) [20]. Paraclinical and neuroimaging studies are also highlighted to demonstrate these changes. Our patient presented laboratory, imaging, and other diagnostic studies within normal limits, consistent with some reports where a similar case was evidenced [15,16,21–23], making it a complex condition to diagnose opportunely. Additionally, some authors suggest that a CT scan early in the disease process may not provide meaningful information [13].

We reviewed the literature in the online database of PubMed, published between January 2000 and January 2023. MeSH terms were used: 'Toxic leukoencephalopathy,' 'methadone intoxication,' 'brain edema,' and 'adverse events.' These terms were linked to the Boolean connectors. Only articles published in English or Spanish were included. The relevant references from the reports for our review were manually searched. The inclusion criteria were articles describing methadone abuse or intoxication, subsequently developing some form of neurotoxicity, also used Naranjo's score [20] for selecting the articles indicated in Table 1 with a score of 4 points. The exclusion criteria included studies not describing neurotoxicity associated with methadone use. Citations, abstracts, and full-text articles were reviewed. We selected nine papers **(Table 1)**. shows the reported cases of methadone-induced encephalopathy, including ours.

The literature mentions that the μ-opioid agonist methadone is used in opioid detoxification and treatment of moderate to severe pain [24]. Its use has been associated with inflammatory processes in the central nervous system, particularly in the cerebellum,

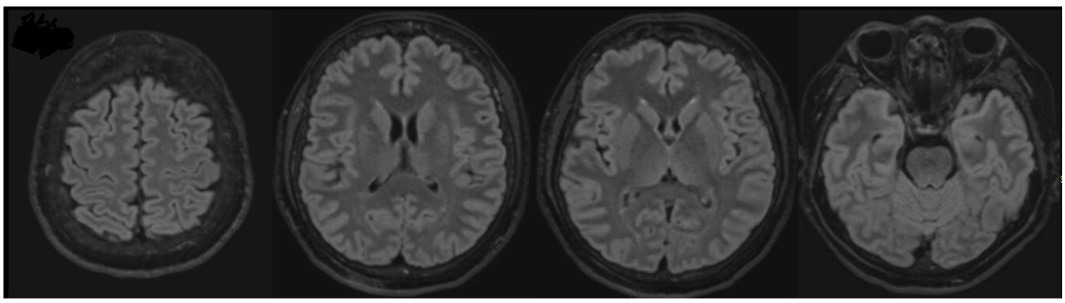

Fig. 2. Several levels of cerebral magnetic resonance without significant pathological findings and resolution of initial cerebral edema.

Table 1
Cases reported of methadone-induced encephalopathy.

No.	Age	Sex	Brain images	Management	Outcome	Ref.
1	9	M	Standard CT, (MRI), symmetric T2-signal abnormalities in the cerebellum and posterior limbs of the internal capsules.	A 5-day course of pulse steroids (IV solumedrol 30mg/kg/d).	The patient was discharged home after a 10-day hospital stay. Clinically asymptomatic.	(16)
2	65	F	(MRI), extensive and symmetric signal-intensity abnormalities in the deep white matter of both cerebral hemispheres.	N/A	In the following month, the patient slowly recovered.	(21)
3	49	M	(MRI), subtle areas of high-signal intensity in the white matter of the right cerebellar hemisphere.	Naloxone, flumazenil, mechanical ventilation, and hemodynamic support.	Three months later, cognitive impairment and neurological symptoms were fully resolved.	(22)
4	15	F	(MRI), diffuse non-enhancing T2 hyperintensities and restricted diffusion in the white matter of both hemispheres.	Mechanical ventilation and hemodynamic support.	Died shortly thereafter because of irreversible cerebral edema.	(19)
5	34	M	(MRI), bilateral parasagittal white matter changes cranial to the ventricles with a "string-of-beads" appearance on T2.	Treated in intensive care for the first eight days and remained at the department of internal medicine for the next seven days.	Upper moderate disability with the ability to perform some previous activities.	(31)
6	49	F	(MRI), bilateral diffuse white matter changes, more pronounced in the frontal and parietal lobes.	Mechanical ventilation and hemodynamic support, needed to be fed through a feeding tube.	She regained normal function of her proximal muscle groups but kept her hands and feet dystonic.	(23)
7	3	F	(MRI), significant bilateral diffuse cerebellar swelling and edema.	30 ml/kg of fluid, mechanical ventilation and hemodynamic support, intravenous acyclovir, erythromycin, ceftriaxone, and amoxicillin for possible meningoencephalitis.	Improved neurologically, had mild spastic diplegia and residual dystonia, and required mobilization with assistance.	(17)
8	54	F	(MRI), hyperintense signal changes in the supratentorial white matter, corpus callosum, and pons with some small vacuoles and mild diffusion restriction	Mechanical ventilation and hemodynamic support; antibiotic and corticosteroid.	She died shortly after the admission.	(15)
9	3	M	(MRI), Bilateral and symmetric hypodensity of the cerebellar hemispheres and pons, acute hydrocephalus.	Mechanical ventilation and hemodynamic support; naloxone and methylprednisolone (30/kg/day) for three days were administered.	Residual ataxia, which resolved in 4 weeks.	(29)
10	53	F	(CT), severe cerebral edema characterized by brain sulcal effacement and diminished ventricular space.	Treated at the intensive care unit, methadone was suspended, and 8 mg of intravenous dexamethasone was started every 8 hours for two days.	Total recovery, no sequelae or neurological alterations.	Our patient

Abbreviations: F, female; *M,* male; *N/A*, Not available; *Ref*, Reference; *MRI,* Magnetic Resonance Imaging; *CT*, Computed tomography.

although generalized forms in the brain have been reported [25]. An encephalopathic effect due to acute use has also been reported with high-dose intravenous administration [26]. Brain damage is chronic and slow [27]. In addition, patients with methadone-induced encephalopathy present with imaging findings that generally involve the cerebellum or basal ganglia [28], while our patient presented with generalized cerebral edema. Additionally, despite the lack of a consensus in treating these patients, according to existing evidence, some reports describe an adequate improvement with corticosteroid therapy [11,16,29], as presented in this article.

Although delayed neurological effects of methadone use are known, acute effects are atypical, and encephalopathy and extrapyramidal effects have been found in methadone intoxication [30]. The occurrence of severe cerebral edema associated with the initiation of oral methadone in our patient raises questions about the potential underlying mechanisms. While the exact pathophysiology remains unclear, it is essential to consider some potential factors. Methadone is a synthetic opioid that interacts with μ-opioid receptors, and its use has been associated with inflammatory processes within the central nervous system, particularly in the cerebellum, although more generalized forms of brain involvement have been reported [25]. The patient presented with generalized cerebral edema; a manifestation not commonly observed following oral methadone administration. Other potential causes of cerebral edema were meticulously excluded, including SLE activity itself, which was inactive in our patient. The rapid onset of cerebral edema upon the introduction of the drug and its swift resolution following withdrawal without subsequent neurological sequelae suggest a direct relationship between oral methadone use and this adverse event. However, further research is warranted to elucidate the precise mechanisms at play. The management of the cerebral edema in our patient involved the discontinuation of methadone and the administration of intravenous dexamethasone. These interventions led to a prompt resolution of neurological symptoms. While our case's management aligns with some existing evidence suggesting the effectiveness of corticosteroid therapy [11,16,29], the specific therapeutic approach to methadone-induced cerebral edema remains a topic of debate within the medical community.

In the case presented, acute cerebral edema is described, which is not frequent after the intake of oral methadone. Other causes of cerebral edema were also ruled out, and when the medication was discontinued, the patient presented symptomatic and neuroimaging improvement. Our case is atypical; cerebral edema occurs rapidly with oral administration of the drug and presents a rapid resolution upon withdrawal without leaving subsequent neurological sequelae.

It's important to acknowledge the limitations of this study. Firstly, being a single-case report, its findings may not be universally applicable. Secondly, the exact mechanisms behind cerebral edema related to oral methadone use remain speculative, and treatment approaches lack consensus. Thirdly, both the association of the neurological condition with the use of methadone related to time and

the clinical improvement with the withdrawal of the medication, are the conditions that allow us to make the inference of an adverse event. There is no specific method to determine this association. Additionally, there may be a possible publication bias regarding the exclusive use of PubMed to conduct our review of the literature and the period from 2000 to 2023. Despite these limitations, this case highlights potential risks associated with opioid medications and the complexities of managing patients with atypical presentations.

4. Conclusion

This case report presents a unique instance of severe cerebral edema associated with the initiation of oral methadone, emphasizing the importance of clinical vigilance when prescribing opioid medications. The patient's prompt recovery upon methadone discontinuation and dexamethasone administration highlights a potential management approach for similar cases. Our findings emphasize the importance of heightened vigilance among clinicians when prescribing and monitoring opioid medications, including methadone when patients present with unexplained neurological symptoms.

Ethics statement

This study was reviewed and approved by Fundación Valle del Lili's Institutional Review Board. The patient provided informed consent to participate in this report.

Data availability statement

The data associated with the study has not been deposited into a publicly available repository. The authors do not have permission to share data.

CRediT authorship contribution statement

Carlos A. Cañas: Writing – review & editing, Validation, Conceptualization. **Ivan Posso-Osorio:** Supervision, Investigation, Data curation. **Robert Rivera-Londoño:** Writing – original draft, Data curation, Conceptualization. **Juan D. Bolaños:** Writing – original draft, Supervision, Formal analysis, Data curation. **Ana M. Granados:** Writing – review & editing, Validation, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

References

[1] B.P. Markovitz, A.C. Duhaime, L. Sutton, et al., Effects of alfentanil on intracranial pressure in children undergoing ventriculoperitoneal shunt revision, Anesthesiology 76 (1) (1992) 71–76, https://doi.org/10.1097/00000542-199201000-00011. PMID: 1729939.
[2] T.L. Sacco, S.A. Delibert, Management of intracranial pressure: Part I: pharmacologic interventions, Dimens. Crit. Care Nurs. 37 (3) (2018) 120–129, https://doi.org/10.1097/DCC.0000000000000293. PMID: 29596288.
[3] T.P. Welch, M.J. Wallendorf, E.D. Kharasch, et al., Fentanyl and midazolam are ineffective in reducing episodic intracranial hypertension in severe pediatric traumatic brain injury, Crit. Care Med. 44 (4) (2016) 809–818, https://doi.org/10.1097/CCM.0000000000001558.
[4] A.S. Keats, J.C. Mithoefer, The mechanism of increased intracranial pressure induced by morphine, N. Engl. J. Med. 252 (26) (1955) 1110–1113, https://doi.org/10.1056/NEJM195506302522602.
[5] C. Weinstabl, N. Mayer, B. Richling, et al., Effect of sufentanil on intracranial pressure in neurosurgical patients, Anaesthesia 46 (10) (1991) 837–840, https://doi.org/10.1111/j.1365-2044.1991.tb09596.x.
[6] T. Donuk, A.E. Altıntoprak, H. Tekin, Possible causal link between idiopathic intracranial hypertension and the misuse of codeine-based products, J. Child Adolesc. Psychopharmacol. 26 (8) (2016) 764–765, https://doi.org/10.1089/cap.2015.0042.
[7] W. Amjad, W.T. Qureshi, A.U. Farooq, Delayed cerebral edema leading to cerebral hernia in a patient with heroin overdose, Am. J. Therapeut. 25 (6) (2018) e752–e755, https://doi.org/10.1097/MJT.0000000000000761.
[8] M.J. Meyer, J. Megyesi, J. Meythaler, et al., Acute management of acquired brain injury part II: an evidence-based review of pharmacological interventions, Brain Inj. 24 (5) (2010) 706–721, https://doi.org/10.3109/02699051003692126.
[9] S.E. Hocker, J. Fogelson, A.A. Rabinstein, Refractory intracranial hypertension due to fentanyl administration following closed head injury, Front. Neurol. 4 (2013) 3, https://doi.org/10.3389/fneur.2013.00003.
[10] M. de Nadal, F. Munar, M.A. Poca, et al., Cerebral hemodynamic effects of morphine and fentanyl in patients with severe head injury: absence of correlation to cerebral autoregulation, Anesthesiology 92 (1) (2000) 11–19, https://doi.org/10.1097/00000542-200001000-00008.
[11] T. Wheaton, B.J. Toll, K. Breznak, et al., Opioid-induced toxic leukoencephalopathy: a case report and review of the literature, Heliyon 5 (12) (2019) e03005, https://doi.org/10.1016/j.heliyon.2019.e03005. PMID: 31879710; PMCID: PMC6920259.
[12] N. Lindsey, Rupa Radhakrishnan Haut, Riad Lutfi, et al., Acute cytotoxic cerebellar edema subsequent to fentanyl patch intoxication in an infant, Case Reports in Critical Care 2021 (2021) 5, https://doi.org/10.1155/2021/9449565. Article ID 9449565.
[13] C.S. Krinsky, R.R. Reichard, Chasing the dragon: a review of toxic leukoencephalopathy, Academic Forensic Pathology 2 (1) (2012) 67–73, https://doi.org/10.23907/2012.009.

[14] A. Sharma, R. Patnaik, H.S. Sharma, Neuroprotective effects of 5-HT3 receptor antagonist ondansetron on morphine withdrawal induced brain edema formation, blood-brain barrier dysfunction, neuronal injuries, glial activation and heat shock protein upregulation in the brain, Int. Rev. Neurobiol. 146 (2019) 209–228, https://doi.org/10.1016/bs.irn.2019.06.011.
[15] A.M.J. Van Esch, A. Fest, B.S. Hoffland, et al., Toxic leukoencephalopathy presenting as lethal catatonia, J. Addiction Med. 13 (3) (2019 May/Jun) 241–244, https://doi.org/10.1097/ADM.0000000000000470. PMID: 30394993.
[16] S. Salloum, I. Reyes, E. Ey, et al., Acute cerebellitis and atypical posterior reversible encephalopathy syndrome associated with methadone intoxication, Neuropediatrics 51 (6) (2020 Dec) 421–424, https://doi.org/10.1055/s-0040-1708547. Epub 2020 Mar 20. PMID: 32198741.
[17] F. Mills, S.C. MacLennan, C.J. Devile, et al., Severe cerebellitis following methadone poisoning, Pediatr. Radiol. 38 (2) (2008 Feb) 227–229, https://doi.org/10.1007/s00247-007-0635-6. Epub 2007 Oct 20. PMID: 17952429.
[18] D. Duran, R.D. Messina, L.A. Beslow, et al., Malignant cerebellar edema subsequent to accidental prescription opioid intoxication in children, Front. Neurol. 8 (2017) 362, https://doi.org/10.3389/fneur.2017.00362. PMID: 28790973; PMCID: PMC5524743.
[19] M. Metkees, I.R. Meesa, A. Srinivasan, Methadone-induced acute toxic leukoencephalopathy, Pediatr. Neurol. 52 (2) (2015 Feb) 256–257, https://doi.org/10.1016/j.pediatrneurol.2014.10.021. Epub 2014 Oct 30. PMID: 25433910.
[20] C.A. Naranjo, U. Busto, E.M. Sellers, et al., A method for estimating the probability of adverse drug reactions, Clin. Pharmacol. Ther. 30 (2) (1981) 239–245, https://doi.org/10.1038/clpt.1981.154. PMID: 7249508.
[21] R.A. Salgado, P.G. Jorens, I. Baar, et al., Methadone-induced toxic leukoencephalopathy: MR imaging and MR proton spectroscopy findings, AJNR Am J Neuroradiol 31 (3) (2010) 565–566, https://doi.org/10.3174/ajnr.A1889. Epub 2009 Nov 5. PMID: 19892815; PMCID: PMC7963967.
[22] A. Cerase, S. Leonini, M. Bellini, et al., Methadone-induced toxic leukoencephalopathy: diagnosis and follow-up by magnetic resonance imaging including diffusion-weighted imaging and apparent diffusion coefficient maps, J. Neuroimaging 21 (3) (2011) 283–286, https://doi.org/10.1111/j.1552-6569.2010.00530.x. Epub 2010 Oct 26. PMID: 20977538.
[23] S. Gheuens, A. Michotte, A. Flamez, et al., Delayed akinetic catatonic mutism following methadone overdose, Neurotoxicology 31 (6) (2010) 762–764, https://doi.org/10.1016/j.neuro.2010.07.007. Epub 2010 Aug 3. PMID: 20688102.
[24] I. Carroll, A.C. Heritier Barras, E. Dirren, et al., Delayed leukoencephalopathy after alprazolam and methadone overdose: a case report and literature review, Clin. Neurol. Neurosurg. 114 (6) (2012) 816–819, https://doi.org/10.1016/j.clineuro.2011.12.052.
[25] J. Repple, S. Haessner, A. Johnen, et al., Intravenous methadone causes acute toxic and delayed inflammatory encephalopathy with persistent neurocognitive impairments, BMC Neurol. 21 (1) (2021) 85, https://doi.org/10.1186/s12883-021-02108-9.
[26] G.Y. Wang, T.A. Wouldes, B.R. Russell, Methadone maintenance treatment and cognitive function: a systematic review, Curr. Drug Abuse Rev. 6 (3) (2013) 220–230, https://doi.org/10.2174/18744737112059990020.
[27] M. Haghighi-Morad, Z. Naseri, N. Jamshidi, et al., Methadone-induced encephalopathy: a case series and literature review, BMC Med. Imag. 20 (1) (2020) 6, https://doi.org/10.1186/s12880-020-0410-9.
[28] M. Mittal, Y. Wang, A. Reeves, et al., Methadone-induced delayed posthypoxic encephalopathy: clinical, radiological, and pathological findings, Case Rep Med 2010 (2010) 716494, https://doi.org/10.1155/2010/716494.
[29] M. Anselmo, A.C. Rainho, M. do Carmo Vale, et al., Methadone intoxication in a child: toxic encephalopathy? J. Child Neurol. 21 (7) (2006) 618–620, https://doi.org/10.1177/08830738060210071101.
[30] S. Shrot, A. Poretti, E.W. Tucker, et al., Acute brain injury following illicit drug abuse in adolescent and young adult patients: spectrum of neuroimaging findings, NeuroRadiol. J. 30 (2) (2017) 144–150, https://doi.org/10.1177/1971400917691994.