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Drug Interaction and Serotonin Toxicity with Opioid Use: Another Reason to Avoid Opioids in Headache and Migraine Treatment

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Abstract Treatment of headache, specifically migraine attacks, has always been a challenging subject, especially for neurologist and pain specialists. Triptans are generally underutilized, despite being the gold standard abortive medication for migraine attacks. On the other hand, opioid analgesics are overused as a treatment for headache. One reason for this could be physician unfamiliarity with drug interactions between opioids and other medications, especially the possibility of serotonin toxicity. The general awareness of potential serotonin toxicity with using opioid analgesics is low. In this review, we will conduct a theoretic and evidence-based review of the potential for developing serotonin syndrome in patients who are using opioids analgesics, especially in combination with antidepressants, a common co-prescribed combination. We also review the current diagnostic criteria for serotonin syndrome and identify possible shortcomings of those criteria. Our aim is to increase the awareness of health care providers about potential drug interaction of opioid analgesics with other classes of medication. We place particular emphasis on tramadol since this drug is one of the most commonly used opioid analgesics for headache. The potential for developing serotonin syndrome is relatively high in the patients who are using opioid for pain control. The use of opioids in migraine headache is already discouraged due to the high risk of medication overuse headache and also an increase in headache-related disability (Katsarava et al. Neurology 62:788–790, 2004; Bigal and Lipton. Neurology 71:1821-8, 2008; Casucci and Cevoli. Neurol Sci. 34 Suppl 1:S125–8, 2013). This is another reason that physicians and health care providers should avoid using this class of medication for pain, specifically headache and migraine treatment.

Keywords Drug interaction · Serotonin syndrome · Opioids · Tramadol · Antidepressants · Headache

Introduction

Although triptans are the gold standard for migraine attacks, they are underutilized. Studies performed in selected populations show that triptan use is low (*3–19 % of migraine patients*) in various countries [1, 2]. Studies analyzing pharmacy databases showed that only 60 % of eligible migraineures receive at least one new triptan prescription over a 12-month period [2, 3].

Insurance companies likely play an important role in the under-utilization and under-prescription of triptans, since a majority are reluctant to cover most triptan formulations [4]. However, concern for potential adverse reactions also plays a significant role. The US Food and Drug Administration (FDA) has a warning about taking SSRIs or SNRIs with triptans due to the potential risk of serotonin syndrome. Multiple reviews purporting the safety of triptans in patients who are also taking SSRI/SNRI have been published over the past few years [5, 6, 7]. As such, this review will not discuss this well-described topic.

In addition, a general lack of awareness in the diagnosis and treatment of migraine is compounded by the ease of the

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prescription of opioids, since they are rarely denied by insurance companies for headache treatment. The result is that opioid analgesics (including tramadol) are a commonly used class of medication for migraine attacks, specifically by emergency physicians, general practitioners, primary care physicians, and pain specialists [8•].

On the other hand, it seems that a general awareness of potential serotonin toxicity with opioid analgesics is low, which may also contribute to the overutilization of this class of medication in pain and headache medicine.

Background

Serotonin or 5-HydroxyTryptamine (5-HT) is a neurotransmitter, which has a remarkable role in several conditions, including pain, headache (e.g., migraine), appetite, sleep, anxiety, mood, and emesis [9].

Also, 5-HT can interact as a co-transmitter with other neurotransmitter systems, such as Noradrenaline and GABA (gamma-aminobutyric acid) [10]. Therefore, it is not surprising that many medications utilized for various medical conditions have some effect on 5-HT, mainly by increasing 5-HT levels. Like any other neurotransmitter, excessive levels of 5-HT can cause adverse effects on the body, some of which can be life threatening.

There are seven known 5-HT receptors, some of which have sub-types. 5-HT receptors are present in both the central and peripheral nervous system and can be presynaptic or postsynaptic.

Hyperstimulation of "*postsynaptic*" mainly 5-HT2A and probably 5-HT-1A receptors, seems to be the major pathophysiologic event for developing a potentially life-threatening condition, called Serotonin Syndrome (SS). This hyperstimulation could occur "directly" due to receptor stimulation, or can occur though "increased intrasynaptic serotonin" level [11]. Triptans are agonists of "*presynaptic*" 5-HT1B and 5HT-1D receptors and are therefore unlikely to play any role in the development of SS, even if they are co-prescribed with antidepressants [5, 6, 7].

SS can develop when a new serotonergic drug is added to the patient's drug regimen, or when the dose is increased [12••]. In some cases, the patient is genetically more susceptible to changes in serotonin level, or may have cytochrome isoform mutations that cause this issue to emerge [13].

5-HT also interacts with the dopaminergic system (DA), facilitating dopamine release, which may contribute to the development of the clinical presentation of SS. 5-HT2A receptors could regulate the activity of DA neurons in the ventral tegmental area (VTA) by acting through 5-HT2A receptors present on non-DA (presumably GABAergic) neurons or directly on DA cells [14]. This probably explains the motor (agitation) and delirium features of SS.

The diagnosis of SS is based on clinical findings. There are no laboratory tests to confirm it; therefore, physicians should be aware of probable causes, and a detailed drug history, in addition to neurologic examinations are essential. Some studies show that this syndrome is often misdiagnosed, and mild cases are often dismissed without suspicion of a possible role for SS in the patient presentation [11, 15].

When facing symptoms of SS, it is essential for physicians to make an accurate diagnosis and avoid missing mild or early cases. Due to diagnostic challenges, three different sets of criteria have been developed: Sternbach, the Hunter serotonin toxicity, and Radomski [16].

Sternbach's is the oldest set of diagnostic criteria for SS and does not include some important symptoms, such as clonus. It also includes some nonspecific features (such as elevated temperature, diaphoresis, and diarrhea). It relies heavily on the patient's mental status, thus allowing, other cause of delirium to be mistaken for serotonin syndrome [16].

Hunter's criteria are simpler and have a comparable specificity but higher sensitivity [17] when compared to Sternbach's criteria (*97 % versus 96 % and 84 % versus 75 %, respectively*). It has gained popularity over the years. In contrast to Sternbach's, within the Hunter criteria, less attention is paid to mental status changes, which can sometimes be a major component of SS (e.g., delirium and coma). The Hunter criteria are perhaps still the most sensitive and accurate tool. Patients taking a serotonergic drug can fulfill this set of criteria if they have at least one of the following five findings [18]:

1. Spontaneous clonus
2. Inducible clonus plus agitation or diaphoresis
3. Ocular clonus and agitation or diaphoresis
4. Tremor and hyperreflexia
5. Hypertonia, temperature above 38 °C and ocular clonus or inducible clonus.

Radomski et al. [10] classified SS into three subtypes, based on the severity of symptoms:

1. Mild state of serotonin-related symptoms
2. Full-blown serotonin syndrome
3. Toxic states

This classification seems to be more practical in clinical setting, and we will discuss this matter further.

The 2014 annual report of the " American Association of Poison Control Centers" mentions many reports that involve overexposure to serotonin. In this report, analgesics (tramadol being in this class) are the most frequent substances that involve human exposure and fatality. The rate of exposure has increased very rapidly in comparison to other classes [19•].

Data Synthesis

For this study, we searched PUBMED, MEDLINE, and EMBASE search engines from 1974 to December 2015. The key words for this search were *serotonin syndrome*, *serotonergic drugs*, *serotonin toxicity*, *opioids*, *opioid analgesics*, *tramadol*, *meperidine*, *codeine*, *oxycodone, fentanyl*, *methadone*, and *morphine*. All English articles that described co-administration of serotonergic drugs and opioids in humans or serotonin syndrome occurrence on opioid analgesic use were included in this study.

Forty-one articles were found, among which three studies were on serotonin syndrome and opioids in general, (*one review published in 1998 and two articles in 2015*) [20, 21••, 22•] and 38 studies specifically discussed one particular opioid analgesic. Of the 38 single opioid studies, 17 (44.7 %) were attributed to tramadol. This was the highest number reported, including 12 case reports (Table 1). Of the 12 case reports, six were due to concomitant SSRI use. There are two reports of tramadol overdose and one report of accidental ingestion.

Following tramadol, meperidine and methadone are the most common reported opioids.

In terms on concomitant agents, as expected, SSRIs and then TCAs, SNRIs, and MAOIs have the highest number of reports. There are a number of lesser-known drugs, such as antipsychotics (Ziprasidone), antibiotics (linezolid, ciprofloxacin), and antiepileptic (pregabalin).

There are two reports of concomitant use of two different opioids causing SS (methadone with fentanyl).

Dextromethorphan was not included in our search because this drug is utilized as a cough suppressant and not as an analgesic [23]. We did not include mixed agonist-antagonists and partial agonists of opioids (e.g., buprenorphine).

In our findings, most cases of SS were due to co-administration of another serotonergic drug. Also, there were several cases of tramadol and methadone solely causing this syndrome when overdosed. In one of the cases we reviewed, the syndrome developed when the fentanyl patch dosing was increased [24].

Discussion

The pharmacology of opioid analgesics in combination with serotonin is slightly different among the various agents due to their different structures. The opioid action, best known for its serotonergic activity, is weak inhibition of 5HT reuptake. But it can also increase the intrasynaptic release of serotonin by its inhibitory effect on GABA-ergic neurons, which in turn, has inhibitory effects on 5HT neurons at presynaptic sites [25].

Opioids can be classified by their structure into four classes: phenylpiperidine, phenanthrene phenylheptylamines (diphenylheptanes), and benzomorphans. Phenylpiperidine are compounds with a variety of pharmacological effects, including morphine-like and "serotonin reuptake inhibitor" properties [26, 27].

Methadone, meperidine, and fentanyl inhibit the reuptake of serotonin. But other opioids, also called phenanthrene analogues of morphine (codeine and oxycodone), are not 5HT reuptake inhibitors. They may increase 5HT levels intrasynaptically through unknown mechanisms [24].

Tramadol is a synthetic opioid with a cyclohexanol structure, which has a unique dual mechanism of action. It acts as selective mu-receptor agonist by its main metabolite, O-desmethyltramadol. One of tramadol's enantiomers (*SS form*)* can act as a norepinephrine and serotonin re-uptake inhibitor and also increases the release of serotonin [28, 29]. Tramadol has been increasingly prescribed in recent years for a variety of pains, including headache. Most physicians prescribe it as an alternative to opioids and believe this drug has a better safety profile, less adverse effects (especially respiratory depression), and lower dependence and abuse rate. Until recently, it was never scheduled. However, in August 2014, the Drug Enforcement Administration (DEA) added tramadol to its category of schedule IV drugs [30].

Table 2 refers to drug combinations which were associated with serotonin syndrome in our search results. Different antidepressants co-administered with all opioid analgesics resulted in SS are listed in this table.

In our review, the reported cases of SS with tramadol [31–33] are significantly higher than other opioid analgesics. This might be due to its variety of dosage forms, particularly the oral form and the fact that this drug was not scheduled until 2014. Also some insurance companies list Tramadol as a non-narcotic analgesic medication, https://www.anthem.com/ca/health-insurance/nsecurepdf/pharmacy_ca_condensed_formulary.pdf which also contributes to its widespread prescription.

When reviewing the basic pharmacology of opioids, tramadol is known for its modulation of serotonin. Therefore, health care providers should be aware of its drug interactions [34]. Another concern with tramadol and serotonergic toxicity is related to Cytochrome P450 system (CYP). Since SSRI's inhibit the 2D6 isoenzyme of CYP and tramadol is also mainly metabolized by this isotype, concomitant use can result in higher levels of tramadol and a greater chance of SS [35].

While overdose of any serotonergic agent could cause serotonin toxicity and SS, the chance that monotherapy with serotonergic opioids, including tramadol, causes SS is probably higher than the antidepressant class. This is due to the habituation feature of opioids, which increases the possibility of *overuse* with this class of medication. In the most recent review of different medication classes that contributed to SS,

Table 1 Literature results of searches for serotonin syndrome and opioid analgesics from 1974 to 2015

Opioid analgesic	Co-administered drug	Type of manuscript	Year of publication
Tramadol	Sertraline	Case report	1997
Tramadol	Fluoxetine	Case report	1999
Tramadol	Serotonin syndrome	Brief report	1999
Tramadol	Citalopram	Case report	2004
Tramadol	Overdose	Case report	2004
Tramadol	Serotonin syndrome	Review article	2005
Tramadol	Serotonin syndrome	Review article	2005
Tramadol	Serotonin syndrome	Review article	2009
Tramadol	Overdose	Case report	2010
Tramadol	Citalopram	Case report	2011
Tramadol	Accidental ingestion by infant	Case report	2011
Tramadol	SSRIs	Case report	2012
Tramadol	Chlordiazepoxide (for preventive effect on tramadol overdose induced serotonin syndrome)	Clinical trial	2013
Tramadol	Ziprasidone	Case report	2014
Tramadol	SSRIs	Case report	2014
Tramadol	Trazodone, oxycodone, bupropion	Case report	2014
Tramadol	Serotonin syndrome	Review article	2015
Meperidine	Moclobamide	Case report	1995
Meperidine	Sibutramine	Case report	2001
Meperidine	Venlafaxine, amitriptyline	Case report	2002
Meperidine	Fluoxetine	Case report	2003
Meperidine	Citalopram	Case report	2007
Meperidine	Linezolid	Case report	2008
Meperidine	Clomipramine	Case report	2015
Oxycodone	Fluvoxamine	Case report	2006
Oxycodone	Citalopram	Case report	2012
Oxycodone	Pregabalin	Case report	2013
Codeine	Sertraline	Case report	1997
Fentanyl	Sibutramine	Case report	2001
Fentanyl	Citalopram	Case report	2007
Fentanyl	Paroxetine	Case report	2008
Methadone	SSRIs	Case report	2006
Methadone	Overdose	Case report	2008
Methadone	Venlafaxine, ciprofloxacin	Case report	2009
Methadone	Duloxetine	Case report	2012
Methadone	Fentanyl	Case report	2015
Methadone	Fentanyl	Case report	2015
Morphine	Phenelzine	Case report	2015

opioids were the second class, following SSRI/SNRI, even higher than MAO inhibitors and TCAs [21••].

Based on our reviewed literature, we think physicians should consider the possibility of SS triggered by common prescribed opioids and the fact that this syndrome can be fatal [12••]. This is more relevant when we consider that patients, who are using opioids on a chronic basis, are more likely to have comorbid depression and increased likelihood of taking some type of antidepressant. A retrospective study showed that 20.7 % of people who received a tramadol prescription also received an antidepressant within 30 days [36].

Since the presentation of SS is extremely variable, physicians can miss the diagnosis, especially when different clinical signs and symptoms are present, when there is altered drug clearance (e.g., in elderly), and due to variable metabolism of

Table 2 Co-administration of different classes of opioids together or with antidepressants which causing serotonin syndrome with its possible mechanisms [1, 16, 17]

Opioid drug	Chemical class	Possible mechanisms of serotonin syndrome	Co-administered serotonergic drug, causing serotonin syndrome
Tramadol	Cyclohexanol	Inhibition of serotonin reuptake Increase of serotonin release	Trazadone, oxycodone, bupropion, citalopram, fluoxetine, sertraline
Methadone	Phenylheptylamines (diphenylheptanes)	Inhibition of serotonin reuptake	Citalopram, fluoxetine, phenelzine, fentanyl, duloxetine, venlafaxine, ciprofloxacin
Meperidine	Phenylpiperidine	Inhibition of serotonin reuptake Increase of serotonin release Activating serotonin receptors	Clomipramine, venlafaxine, amitriptyline, citalopram, fluoxetine, moclobamide
Oxycodone	Phenantheren	Increase of serotonin release	Fluvoxamine, citalopram
Fentanyl	Phenylpiperidine	Activating serotonin receptors	Citalopram, paroxetine
Morphine	Phenantheren	Probably increase of serotonin release	Phenelzine

serotonin in patients. Since to date, the best treatment for this syndrome is prevention, a detailed patient drug history is essential. Drugs like SSRIs, SNRIs, TCAs, and MAOIs, illicit drugs from amphetamine family, cold and flu medications containing dextromethorphan, some weight loss medications, some antibiotics (e.g., linezolid), and herbal medicine (e.g., St. John's wort) can increase the risk of SS [28, 37–39] and need to be considered during history taking.

In terms of exam, it is very helpful to conduct some simple neurological tests, including tremor, deep tendon reflexes and tone, in patients who are at risk for developing serotonin toxicity, since those findings could indicate early signs of serotonin excess.

Identification of patients in the earlier stages of serotonin excess can prevent developing a more severe toxicity and in turn, SS. Despite the fact that there are several sets of criteria for serotonin syndrome, it seems all methods detect patients who are in the advance stages of serotonin toxicity. Radomski et al. [10] and later on Dunkley et al. [18] and Vopli-Abadie et al. [12••] tried to modify the classification of SS based on its intensity and used the term "*serotonin toxicity*," due to the wide range of its manifestations. We believe this is very

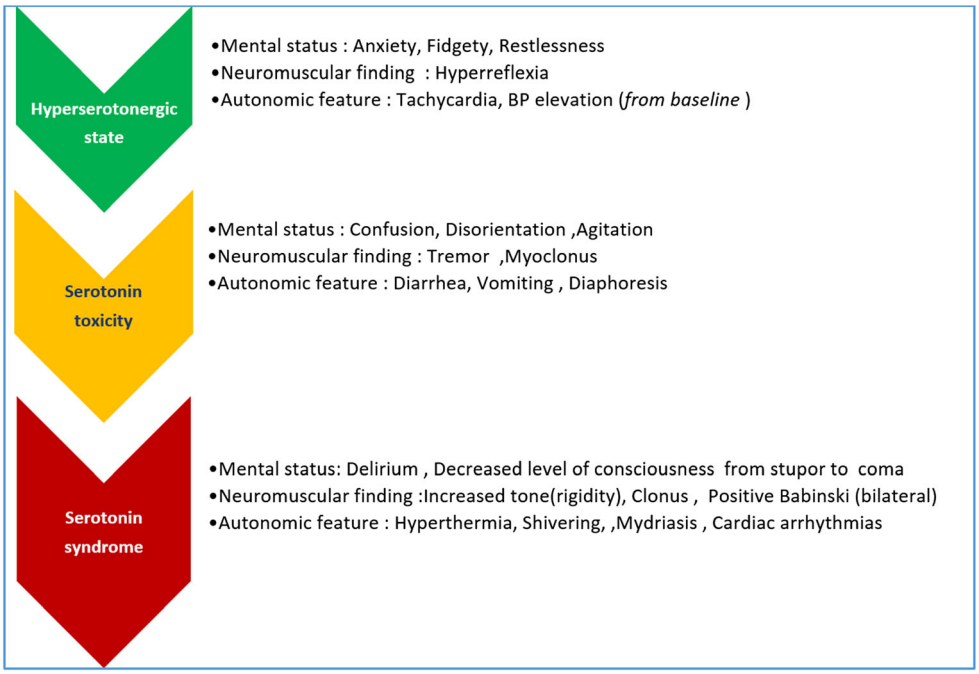

Fig. 1 Clinical spectrum of serotonin excess based on three major triad: *mental status changes*, *neuromuscular finding*, and *autonomic feature*

important, since to date, the best treatment of SS is prevention. Missing the early detection and diagnosis of serotonin toxicity by health care providers can have a potentially life-threatening consequence, which is serotonin syndrome.

Conclusion

Health care providers need to be aware of potential serotonin toxicity and serotonin syndrome, which can occur with opioid medication, especially with concomitant use of antidepressants. This is more important in certain types of opioids, particularly tramadol.

It has already been shown that using opioid analgesics for the treatment of migraine headache, causes a high risk for developing "medication overuse headache" and also increases "headache related disability" [40–42]. Therefore, beside these well-known risks, the risk of serotonin toxicity is another reason that this class of medication should be avoided as much as possible in the treatment of headache, especially migraine.

Because of the package insert warning, many health care providers have concerns about concomitant/concurrent use of antidepressants, like SSRIs/SNRIs with triptans, but not with concomitant use with opioids, while the evidence supports only the latter, not the former. This is may be a possible explanation for under-utilization of triptans in patients with migraine.

Also, due to a lack of knowledge about the serotonergic properties of most opioids, mild cases of serotonin toxicity may be under-diagnosed and severe cases may be misdiagnosed as another condition. Patients who are using any type of serotonergic opioids, especially if they also use other serotonergic agents like antidepressants, are at greater risk for serotonin excess. This is particularly important since early detection of serotonin toxicity is key to avoid developing the potentially life-threatening serotonin syndrome.

We recommend looking at serotonin excess as existing within a spectrum of three stages, as shown in Fig. 1. Since this is not a distinct classification, there can be an overlap of signs and symptoms between stages. The potential benefit of using this spectrum will be the early detection of mild cases of serotonin excess before developing the catastrophic SS.

Acknowledgment *Some drugs are available in different structures, much like left and right hands. These structures that mirror each other are called *enantiomers* and have different binding to receptors, different desired effects, etc. There are four possible combinations for each molecule (SS, RR, RS, SR).

Compliance with Ethical Standards

Conflict of Interest Hossein Ansari declares that he is on the Speaker's Bureau for Teva Pharmaceutical and Avanir Pharmaceutical.

Leila Kouti declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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