PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Perioperative Pain and Addiction Interdisciplinary Network (PAIN): Protocol of a Practice Advisory for the Perioperative Management of Buprenorphine using a Modified Delphi Process
AUTHORS	Goel, Akash; Azargive, Saam; Weissman, J. S.; Shanthanna, Harsha; Ladha, Karim; Lamba, Wiplove; Duggan, Scott; Hanlon, John; Di Renna, Tania; Peng, PW; Clarke, Hance

VERSION 1 - REVIEW

REVIEWER	Anna Lembke Stanford University School of Medicine, USA
REVIEW RETURNED	25-Oct-2018

GENERAL COMMENTS	1. The aim of the authors is to develop consensus guidelines on the optimal perioperative management strategies for patients on buprenorphine. This is a laudable and important goal. 2. In the opening sentence, the authors write: “The ongoing opioid epidemic has necessitated increasing prescriptions of buprenorphine, which is intended to reduce opioid cravings and harms associated with unsafe opioid administration.” I would urge the authors to describe buprenorphine as “treatment for opioid use disorder.” It is not merely a way to reduce cravings and harms. Just as people with diabetes need insulin, people with severe opioid use disorder need opioid agonist therapy. Please consider changing to something like “… has necessitated increasing prescriptions of buprenorphine, which is evidence-based treatment for opioid use disorder, and also shown to reduce harms associated with unsafe opioid administration.” 3. Dividing the analysis by diagnosis group - Opioid Use Disorder Only, Opioid Use Disorder with Co-occurring Pain Disorder, and Pain Disorder- is an excellent idea. 4. Please also consider the public health harm of prescribing full opioid agonists to buprenorphine patients post-operatively, who then go on to be on both buprenorphine and full agonists long term, or leave full agonists lying around for others to find, or give away or sell their pills.

REVIEWER	E. Nalan Ward, MD Massachusetts General Hospital Department of Psychiatry Boston, MA , USA
REVIEW RETURNED	12-Nov-2018

GENERAL COMMENTS	I would like to point out to couple publications on this subject. 1-Alford D, Compton P, Samet J. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. Ann Intern Med. 2007;48:127-134. 2-Ward N, Quaye AN, Wilens T: Opioid Use Disorders: Perioperative Management of a Special Population. Anesth Analg. 2018 Aug;127(2):539-547 PMID: 29847389 There are few important issues that are not explicitly described in the manuscript and not clear if they will considered as clinical characteristics under sections. 1-Those with co-occurring substance use disorders or psychiatric conditions (the comorbidity rates are high among OUD patients, such as AUD, Depression and Anxiety Dx), require individualized approach where pain and co-occurring disorders need to be managed in an integrated fashion. There is benefit in pre-operative screening of comorbid conditions. Comorbid conditions will impact decisions regarding buprenorphine before and after surgery. 2- There is an increased risk of opioid overdose during perioperative phase. I believe it is imperative that any guideline that is developed need to address identifying those at risk for opioid OD and management strategies during periop phase. 3-Patient perspective: It is not clear how patient perspective will be included. What is the method to collect patient opinions? Patient surveys? 4-Post-op pain sections only questions analgesic medication management options. I wonder if the role of behavioral interventions should be included here. 5- Will the guideline include pregnant patient population? Overall, developing such a guideline re: management of buprenorphine during periop phase is very timely to say the least. A patient centered approach is essential to safely treat patients with OUD. As important as it is, the decision about whether to stop, continue or taper buprenorphine can not be done in isolation, and patients need to be approached as a whole.

VERSION 1 – AUTHOR RESPONSE

Response to the Reviewers' Comments to Author

Reviewer: 1

Reviewer Name: Anna Lembke

Institution and Country: Stanford University School of Medicine, USA

Please state any competing interests or state ‘None declared’: None declared.

1. The aim of the authors is to develop consensus guidelines on the optimal perioperative management strategies for patients on buprenorphine. This is a laudable and important goal.

Thank you for acknowledging our efforts, Dr. Lembke. We have followed your work at Stanford very closely and understand the challenges in this area of research.

2. In the opening sentence, the authors write: “The ongoing opioid epidemic has necessitated increasing prescriptions of buprenorphine, which is intended to reduce opioid cravings and harms associated with unsafe opioid administration.” I would urge the authors to describe buprenorphine as “treatment for opioid use disorder.” It is not merely a way to reduce cravings and harms. Just as people with diabetes need insulin, people with severe opioid use disorder need opioid agonist therapy. Please consider changing to something like “… has necessitated increasing prescriptions of buprenorphine, which is evidence-based treatment for opioid use disorder, and also shown to reduce harms associated with unsafe opioid administration.”

Thank you Dr. Lembke for your comments – we have addressed these comments in the updated manuscript to reflect your very appropriate suggestions. You will notice that our opening line in the introduction of the abstract has been modified.

3. Dividing the analysis by diagnosis group - Opioid Use Disorder Only, Opioid Use Disorder with Co-occurring Pain Disorder, and Pain Disorder- is an excellent idea.

Thank you – this was a challenging aspect of the guideline development process and we agreed that it was important to address these three groups.

4. Please also consider the public health harm of prescribing full opioid agonists to buprenorphine patients post-operatively, who then go on to be on both buprenorphine and full agonists long term, or leave full agonists lying around for others to find, or give away or sell their pills.

Thank you for your comments in this regard. We agree that the improper use/disposal of full mu-agonists forms a large part of the ongoing opioid crisis. To your point, we have acknowledged this in our introduction (paragraph 2) and will strive to discuss this important perspective in the final guideline document.

Reviewer: 2

Reviewer Name: E. Nalan Ward, MD

nstitution and Country: Massachusetts General Hospital, Department of Psychiatry, Boston, MA, USA

Please state any competing interests or state ‘None declared’: None declared

I would like to point out to couple publications on this subject.

1-Alford D, Compton P, Samet J. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. Ann Intern Med. 2007;48:127-134.

2-Ward N, Quaye AN, Wilens T: Opioid Use Disorders: Perioperative Management of a Special Population. Anesth Analg. 2018 Aug;127(2):539-547 PMID: 29847389

Thank you Dr. Ward for pointing out these references. Reference number 2 came out during the initial production of the manuscript so unfortunately did not make its way into our background. We have made an effort to include this paper in our background now as it appropriately captures the most up to date perspectives on this important topic.

We have referenced this paper in our introduction (paragraph 2) and also think it would be worthwhile to reference its recommendations in the final guideline document.

There are few important issues that are not explicitly described in the manuscript and not clear if they will considered as clinical characteristics under sections.

1-Those with co-occurring substance use disorders or psychiatric conditions (the comorbidity rates are high among OUD patients, such as AUD, Depression and Anxiety Dx), require individualized approach where pain and co-occurring disorders need to be managed in an integrated fashion. There is benefit in pre-operative screening of comorbid conditions. Comorbid conditions will impact decisions regarding buprenorphine before and after surgery.

Thank you for this great suggestion – indeed buprenorphine-naloxone is viewed by many of these patients as a life-saving medication in the context of a life-long disease. Screening of co-occurring disorders is absolutely essential and ought to be an important aspect of any final guideline document which includes recommendations on the perioperative management of OUD.

In fact, our Delphi process includes the option for written and modified feedback from the panellists and steering committee in order to integrate this type of idea into the final guideline document. We agree that this was not necessarily 'explicit' in our guideline protocol, but fully expect to honour these kinds of recommendations in the final document. We have included a modified phrase in the section entitled 'Delphi Procedures (Data collection and Data analysis)' to emphasize the importance of lending flexibility to our experts in noting where individualized approaches are required in the final guideline document.

2- There is an increased risk of opioid overdose during perioperative phase. I believe it is imperative that any guideline that is developed need to address identifying those at risk for opioid OD and management strategies during periop phase.

Thank you for this comment Dr. Ward, one of the reasons this work is of major importance is not only the risk of perioperative overdose but the lack of insight that the perioperative world has the life long battle that many patients stabilized with buprenorphine have had. Over the past years patients would have this medication stopped likely incorrectly (see our systematic review published in the CJA – ref # 36) due to the misguided fear of poor pain control. Embedded in our rationale to carry out the guidelines, is to stress that destabilization risks patients return to their previous substance abuse which has significant negative consequences and certainly can lead to overdose and death in the peri- and postoperative setting. We have added this insightful angle into the introduction of the current manuscript.

3-Patient perspective: It is not clear how patient perspective will be included. What is the method to collect patient opinions? Patient surveys?

Thank you Dr. Ward – we completely agree with your thoughts on this. We believe that the strength of a strong patient-centered guideline includes the perspectives of both patients and allied health care professionals that are deeply involved in the delivery of high quality care.

We included patients on our expert-panel and on the guideline development process (the modified Delphi process). Mr. Michael Satok-Wolman (our patient representative) agreed to be included as an author on the final guideline document and was helpful in arranging the different sections of the round 1 rater forms. Michael also acted as an expert panellist in the rating of the Round 1 forms. Subsequently, he also participated in the Round table discussion before Round 2, where his comments and perspectives were integrated into the development of the guidelines. Michael has struggled with management of his buprenorphine dose during previous perioperative experiences, and as such, was able to provide appropriate insight throughout this process.

Moreover, we have also included Kari Van-Kamp, a Nurse practitioner with experience in the screening of co-occurring disorders (anxiety, depression) in the context of OUD in order to address your earlier points.

4-Post-op pain sections only questions analgesic medication management options. I wonder if the role of behavioral interventions should be included here.

We agree this is very important and will address this in the final guideline document to ensure that both pharmacological and non-pharmacological behavioural interventions are addressed as options in the perioperative period.

One of our sections is entitled 'involvement of outpatient provider' includes provisions (by virtue of our second round in the Delphi process) to address the possibility of perioperative behavioural interventions. In the section entitled 'Round 1 & 2 of Delphi Procedure' you'll notice we have highlighted in red 'Furthermore, they will be urged to consider patient populations that will require individualized approaches to the management of their buprenorphine dose in the perioperative period'. This is intended to describe exactly the scenario that you have described.

5- Will the guideline include pregnant patient population?

Indeed, our preference is to make this document as inclusive as possible. The Obstetrical world is currently struggling with whether patients should be initiated on methadone vs. buprenorphine. We had considered including pregnant patients in our guidelines but due to the complex nature of developing a set of guidelines which can be useful to all, we decided to focus on general perioperative guidelines and will now consider your advice and potentially integrate expert obstetrical perspectives in future editions of this iterative process.

We feel as though the current protocol will render a final document that all anesthesiologists can easily handle, while at the same time improving the outcomes of this often marginalized population.

Overall, developing such a guideline re: management of buprenorphine during periop phase is very timely to say the least. A patient centered approach is essential to safely treat patients with OUD. As important as it is, the decision about whether to stop, continue or taper buprenorphine can not be done in isolation, and patients need to be approached as a whole.

Once again we thank you Dr. Ward for your thoughts and comments. The decision to start / stop / taper etc. is a certainly not one to be made for a single individual. The guidelines will draw on in a co-ordinated manner from the inputs of anaesthesiologists, psychiatrists, addiction medicine physicians, family medicine physicians, nurse practitioners and patients. Patient centered care is at the focus of our health care system and we certainly stand by those principles.

It is our hope that the protocol we outlined describes flexibility in the development of these guidelines so that some of the points you have raised can be included in the eventual document.

Our aim at formulating this protocol was not to be limiting – in fact, we tried to be as inclusive as possible. Your suggestions will go a long way in incorporating important ideas in the final guideline.

VERSION 2 – REVIEW

REVIEWER	Nalan Ward, MD Massachusetts General Hospital Department of Psychiatry Boston, MA USA
REVIEW RETURNED	11-Feb-2019

GENERAL COMMENTS	I encourage authors to use a nonstigmatizing language and use formal DSM V nomenclature when referring to patient conditions and treatment options.

	Page 19, Line 19:...opioid detoxification, addiction therapy and.... Consider replacing "detoxification" with medically supervised withdrawal Consider replacing addiction therapy with treatment of Opioid Use Disorder (OUD) . Buprenorphine /naloxone only has indication to treat OUD, not other SUDs. Page 20, Line 3.. addiction patient population.. Replace with patients with OUD Page 20, Line 14 and 16: replace substance use disorder with opioid use disorder. Page 20, Line 29-30:.. the destabilization of a patient with a previous substance abuse problem risks the patient returning to their previous life struggle. Consider " ...the destabilization of a patient with an opioid use disorder risks the patient returning to drug use. ". Page 20, Line 54: Risk of worsening of substance use disorder... Replace with 'risk of worsening of opioid use disorder"

VERSION 2 – AUTHOR RESPONSE

Reviewer's Comments to Author:

Reviewer: 2

Reviewer Name: Nalan Ward, MD

Institution and Country: Massachusetts General Hospital, Department of Psychiatry, Boston, MA USA

Please state any competing interests or state ‘None declared’: None declared

I encourage authors to use a nonstigmatizing language and use formal DSM V nomenclature when referring to patient conditions and treatment options.

Thank you very much for these suggestions. We wholeheartedly agree with the need to destigmatize readers with respect to this patient population. Therefore we have included all of the suggestions below in the current revision.

Page 19, Line 19:...opioid detoxification, addiction therapy and....

Consider replacing "detoxification" with medically supervised withdrawal

Consider replacing addiction therapy with treatment of Opioid Use Disorder (OUD) .

Buprenorphine /naloxone only has indication to treat OUD, not other SUDs.

Page 20, Line 3.. addiction patient population..

Replace with patients with OUD

Page 20, Line 14 and 16: replace substance use disorder with opioid use disorder.

Page 20, Line 29-30:.. the destabilization of a patient with a previous substance abuse problem risks the patient returning to their previous life struggle.

Consider " ...the destabilization of a patient with an opioid use disorder risks the patient returning to drug use. ".

Page 20, Line 54: Risk of worsening of substance use disorder...

Replace with 'risk of worsening of opioid use disorder"

Thank you for the opportunity once again to have our work resubmitted and we and we look forward to the upcoming publication in BMJ OPEN.