Peer Review File

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Reviewer A

The authors present the discussion of two case reports that cover a topic that is of high interest for the field of palliative medicine, because currently, we are struggling towards new approaches correctly identifying and dealing with addictive or pseudo-addictive behavior.
The manuscript is written concisely and comprehensively. EQUATOR guidelines are met, though I did not perform a point-by-point check. Semantic, orthography and language in general is impeccable, but please notice, that I am not a native speaker. Relevant literature is cited, though the authors may consider referring to easy-to-follow clinical recommendations, if reference count permits (PMID: 31431028). I completely agree with the conclusion, that positive CAGE screening must not lead to undertreatment of pain, even though we are all aware of the potential hazards of opioid therapy, as it became terribly obvious during the ongoing opioid-crisis.
Line 58: “Space” missing after «symptoms»
Reply: Thank you for pointing out this error. The manuscript is updated accordingly on
On Page 2, Line 58.

Line 106: I believe it should be one “s” less in “missidentified”
Reply: Thank you for pointing out this error. The manuscript is updated accordingly on Page 5, Line 103.

Line 159: “a” missing in “encourged"
Reply: Thank you for pointing out this error. The manuscript is updated accordingly on Page 7, Line 153.

Line 161: “Space” missing after “nausea.”
Reply: Thank you for pointing out this error. The manuscript is updated accordingly on Page 7, Line 155.

Line 168: “irrate”?
Reply: Thank you for pointing out this error. The manuscript is updated accordingly on Page 7, Line 162.

Line 202: “Space” missing after “case,”
Reply: Thank you for pointing out this error. The manuscript is updated accordingly on Page 9, Line 194.

Line 215: “Space” missing after “Additionally,”

Reply: Thank you for pointing out this error. The manuscript is updated accordingly on Page 9, Line 205.

Line 216: “malignancies” (plural)?
Reply: We appreciate the reviewer’s comment. We modified the statement.
Page 9, Line 205, the manuscript now reads as follows:
“Additionally, the patient's male gender, young age, and poor socioeconomic status **with his** advanced malignancy are known risk factors for NMOU behaviors”

Line 223: “.” Missing after (13,14)
Reply: Thank you for pointing out this error. The manuscript is updated accordingly on Page 9, Line 212.

Reviewer B

This case report sought to describe two cases that highlight the limitations of the CAGE-AID in identifying nonmedical use of opioids.

Major comments:

1. Overall, I am of mixed feelings on this report. I believe the language needs to be tempered a bit as this feels like a commentary on the CAGE-AID screener methodology rather than a commentary on its inappropriate use by clinicians or associated implementation issues, such as not discussing results of the CAGE-AID with patients to clear up potential contradictions.
Reply: We appreciate the reviewer’s valuable comment and agree that case-1 highlights the provider’s preoccupation and interpretation of CAGE-AID score as NMOU rather an aid in discussing the potential problem with the patient.

Page 6, Lines 122-127, the manuscript now reads as follows:
“Our PC providers discussed the CAGE-AID results with his wife, who expressed that the patient never had any alcohol or illicit drug-related problems. The patient consumed alcohol only during social events in limited amounts. In addition, the patient perceived his rare use of alcohol negatively and felt guilty that it might have contributed to his cancer diagnosis.”

Page 8, lines 175-179,

“Many screening tools, such as the CAGE-AID questionnaire, the Screener and Opioid Assessment for Patients with Pain questionnaire (SOAPP), and the Opioid Risk Tool (ORT), are used to identify patients at risk for NMOU or SUD, and are recommended by multiple pain guidelines to be used before initiating opioids. Although the administration of these tools is quick and effective, the results must be interpreted with caution as these are meant for screening rather than diagnosing NMOU.(6)”

Page 8, lines 182-185

“The providers were concerned about the positive CAGE-AID score as a risk-factor and that the reported uncontrolled pain and demand for frequent opioids was related to NMOU, delaying the escalation of opioids which resulted in poor pain control.”

2. I agree with the authors that the CAGE-AID lacks validation specifically for NMUO, but I also do not believe that was the intent of the screener (If it was, please include that in the text). The CAGE-AID seems to identify substance use history, which is a well-established risk factor for engaging in NMUO. But risk does not mean inevitability. So there will always be limitations to screener effectiveness. A screener to identify substance use history is relevant, but it should not be the only arbiter of risk. The larger issue is why clinicians, at least as it is seemingly presented here, are only relying on this tool rather than leveraging the tool for patient conversations about substance use behaviors. Rather than saying the “CAGE-AID questionnaire may not accurately identify patients at risk for NMOU” seems superfluous if that was not it’s intention. It may be more accurate to say that “clinicians should not rely solely on the CAGE-AID to identify patients at risk for NMOU”

Reply: We appreciate and agree the reviewer’s valuable comments. The manuscript is now updated as below.

Page 9, Lines 191-193:

“The CAGE-AID questionnaire is highly sensitive but not specific.(6) The results of screening tools must be interpreted with caution and should not supersede the clinician’s judgment. Clinicians should not rely solely on the CAGE-AID to identify patients at risk for NMOU. A positive CAGE-AID implies that the patient is at risk for NMOU but does not establish the diagnosis.”

Other comments:

3. For Case Report 1, the discussion mentions that the individual answered “yes” about problematic alcohol use “due to his concern that even rare consumption…may have contributed to his cancer diagnosis.” However, this was not mentioned in the actual Case Report. When was this information determined? Directly following the CAGE-AID score or at some later date after the treatment plan was developed?

Reply: We appreciate the reviewer’s valuable comments. The manuscript is now updated.

Page 5, Lines 115-116:

“Previously, his CAGE-AID questionnaire (3 of 4 questions) was positive for alcohol consumption, indicating that he was at risk for NMOU.”

Page 6, Lines 122-127, the manuscript now reads as follows:

“Our PC providers discussed the CAGE-AID results with his wife, who expressed that the patient never had any alcohol or illicit drug related problems. The patient consumed alcohol only during social events in limited amounts. In addition, the patient perceived his rare use of alcohol negatively and felt guilty that it might have contributed to his cancer diagnosis.”

4. The conclusion states the CAGE-AID should not be used to "diagnose NMOU." As a screener, I do not believe that was the intent of the tool. This needs some added language to clear up that these are clinician implementation issues rather than a methodological flaw of the CAGE-AID.

Reply: We appreciate the reviewer's comments. We have now updated the manuscript as follows:

Page 10 Lines 214-218

"One limitation of the CAGE-AID is that there is not much evidence to support its use to identify NMOU or SUD among patients with cancer diagnosis. More research is needed in validating screening tools for NMOU in this patient population."

Page 10, Lines 221- 222

"Our cases highlight that the CAGE-AID questionnaire should be used only as a screening tool and not to diagnose NMOU. Clinicians should be aware that the implementation of such screening tools is mainly to identify the risk factors for NMOU. It is essential to interpret its results and other screening tools with caution and in conjunction with clinical findings, regular monitoring of PDMP, and conducting random urine drug screens."

5. The authors highlight in conclusion that risk assessments should be multifaceted. Screeners are not expected to have a 100% rate of success. There will always be variability, particularly with questions on substance use that patients may be hesitant to honestly respond to. Providing two case reports does not negate the utility of the CAGE-AID, or even that it is deficient. More substantial data would be needed to make the argument that its utility is questionable. As noted above, the deficits appear to be in clinician implementation of the screener and risk assessment strategies.

Reply: We appreciate the reviewer's comments. We have updated the manuscript as below:

Page 10, Lines 221- 222

"Our cases highlight that the CAGE-AID questionnaire should be used only as a screening tool and not to diagnose NMOU. Clinicians should be aware that the implementation of such screening tools is mainly to identify the risk factors for NMOU. It is essential to interpret its results and other screening tools with caution and in conjunction with clinical findings, regular monitoring of PDMP, and conducting random urine drug screens."