Editorial

Anticipatory nausea: current landscape and future directions

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Submitted Jul 19, 2016. Accepted for publication Aug 04, 2016.
doi: 10.21037/apm.2016.10.01
View this article at: http://dx.doi.org/10.21037/apm.2016.10.01

Anticipatory nausea (AN) is thought to be a classically conditioned response to previous poor control of chemotherapy-induced nausea and vomiting (CINV). Prior to the introduction of 5-HT3 receptor antagonists in the early 1990s, which revolutionized CINV management, AN incidence rates were as high as 30% (1,2). As the management of CINV continues to improve due to the introduction of additional classes of anti-emetics, we have seen the rates of AN incidence decline over time. This can be clearly seen in the AN rates reported in the largest study to date of AN and CINV incidence titled "Anticipatory Nausea, Risk Factors, and Its Impact on Chemotherapy-Induced Nausea and Vomiting: Results from the Pan European Emesis Registry Study" (3).

In the most recent issue of the *Journal of Pain and Symptom Management*, Molassiotis *et al.* have evaluated likely risk factors for the development of AN and have assessed its impact on CINV development. They have shown the bidirectional relationship between CINV and AN, whereby AN is a consistent predictor of CINV in the subsequent cycle, and previous CINV is the strongest predictor for future AN. It should be noted that the study found that in the first cycle of chemotherapy, the only significant predictors for AN were metastatic disease and anxiety. Upon further examination, it could be suggested that these patients with metastatic disease were more likely to have prior chemotherapy and thus had already developed AN as a result of previous chemotherapy experiences. Therefore, this study demonstrates the strong relationship between CINV and AN.

This paper also highlights the broad steps we have taken forward in reducing AN incidence. Molassiotis reports an incidence of 8% to 14%, with a noticeable trend of increasing AN in later cycles. This lower prevalence is in line with other recent work in South-East Asia that reported an incidence of clinically significant AN at 10% (4,5). However, despite the encouraging incidence rates reported, this was a secondary analysis of trial with different purpose. There continues to be need for large studies designed specifically to evaluate efficacy of AN prevention and management.

There are several additional avenues of research that remain to be explored. First, Molassiotis has shown that AN, continues to be a problem in one in ten patients over the course of therapy despite the use of highly effective classes of CINV prevention agents. One avenue of research will be to continue improving CINV management. Since nausea continues to be one of the most distressing side effects that impact quality of life (6,7), improved nausea control is a reasonable target. There has been recent interest in olanzapine, an antipsychotic agent use to manage breakthrough CINV that has been shown to be an effective agent to reduce nausea (8). However, current research uses high doses, usually 10 mg per day which results in severe sedation that make treatment less tolerable to patients. Future research is needed for smaller doses of olanzapine to better manage breakthrough CINV and thus prevent the development of AN while reducing the high sedation rates.

Secondly, although previous CINV predicts subsequent AN, there continues to be questions as to how we can predict which will patients develop CINV or AN and thus benefit the most from the implementation of prophylactic strategies to prevent occurrence. Systematic implementation of AN management strategies such as prescribing pharmacological agents or providing nonpharmacological measures through sustainable means continues to be a challenge in clinical practice. Despite the association between anxiety and CINV and AN and research

indicating the effectiveness of a variety of psychological interventions to prevent CINV and AN, these techniques are not consistently employed likely due in part to limited resources.

With better identification of patients at risk of CINV or AN, there is opportunity to provide more intensive nonpharmacological interventions to the small group of at-risk patients. This has the added benefit of reducing the need for benzodiazepines, particularly for frail populations that have a high risk of falls.

Finally, the cornerstone of AN prevention is CINV prophylaxis. Current guidelines focus on the risk of CINV development as a result of chemotherapy, but ignore patient-specific factors that have been shown to be significant in CINV development such as age, gender, history of motion sickness or pregnancy-induced nausea/vomiting and psychological well-being. More research is needed in determining how we will systematically incorporate both the chemotherapy treatment risk and patient-specific risk of CINV into primary CINV prophylaxis decisions, thus resulting in a reduction in CINV and subsequent AN.

In conclusion, while this study illustrates the importance of effective CINV prevention in order to reduce the risk of AN, it also demonstrates that nausea continues to be an elusive symptom that has a significant impact on quality of life. Future research needs to consider the effectiveness of nonpharmacological strategies and how best to implement approaches in pragmatic clinical trials.

Acknowledgements

None.

Cite this article as: Ahrari S, Chow R, Goodall S, DeAngelis C. Anticipatory nausea: current landscape and future directions. Ann Palliat Med 2017;6(1):1-2. doi: 10.21037/apm.2016.10.01

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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