INTRODUCTION

In the second half of the last century, dopamine D2-receptor antagonists were a mainstay of the management of post-operative nausea and vomiting (PONV). However, at the start of the 21st century, they sharply declined in popularity, primarily as a result of growing safety concerns, not least of which was the imposition by the US Food and Drug Administration (FDA) of a black box warning on the most widely used agent in the class, droperidol.

Currently there is renewed interest in this class of medications related, in part, to the introduction of a new agent, amisulpride, which was approved by the FDA for the prevention and treatment of PONV in 2020 and is the only approved agent for rescue treatment after failed prophylaxis.

Re-evaluation of the evidence around D2-antagonists suggests they are not interchangeable in terms of either safety or efficacy, as this is an unusually heterogeneous class of drugs. There are at least three distinct structural sub-classes—substituted benzamides, butyrophenones and phenothiazines—with a wide range of pharmacologic properties and side effect profiles (Table 1).

SAFETY

D2-antagonists originally used as antiemetics were classical neuroleptics and first-generation antipsychotics (FGA). Central nervous system (CNS) penetration by D2-antagonist antiemetics results in a wide range of effects. Sedation and neuropsychiatric effects such as dysphoria or cognitive impairment can occur. Extrapyramidal symptoms (EPS) include tardive dyskinesia, dystonia, and akathisia. Neuroleptic malignant syndrome (NMS) presents with fever, mental status changes, muscle rigidity, and autonomic instability, and antagonism of D2-receptors in the pituitary results in hyperprolactinemia. In addition, binding to potassium ion channels can result in QT prolongation and torsade de pointes. Amisulpride is an “atypical” or second-generation antipsychotic with less brain penetration than FGAs, resulting in a lower incidence of these adverse effects.

Although some of the side effects of D2-antagonists are dose-dependent, toxicity exists, and evidence is lacking on the impact of dose reduction on efficacy. Moreover, despite a reduction in frequency, adverse reactions like tardive dyskinesia, dysphoria, or torsade de pointes can have a high impact on patients. The crude incidence rate may not properly reflect the clinical burden. Therefore, it is essential to understand the relative risks of the available D2-antagonists in order for providers to make optimal prescribing decisions.

BENZAMIDES

Amisulpride is a substituted benzamide D2-antagonist and 5-HT2B and 5-HT7A serotonin antagonist with low blood-brain barrier penetration and lower affinity for adrenergic, histamine, and cholinergic receptors, resulting in a lower incidence of anticholinergic and sedative effects. Amisulpride also has preferential binding in the limbic system, resulting in a lower incidence of EPS. A 2020 Cochrane network meta-analysis reported that amisulpride had a comparable incidence of adverse events as compared to placebo. Elevated prolactin levels from amisulpride do not exceed the norm for nonpregnant women, and amisulpride does not meaningfully prolong the QT interval at doses used for PONV management due to its weaker affinity for potassium channels. Recent studies have shown that amisulpride is effective in both preventing PONV and as rescue treatment for PONV. Another benzamide D2-antagonist is metoclopramide, which is a weak D2 and 5-HT3 antagonist with dose dependent side effects that include sedation, EPS, and GI upset due to stimulation of gastric smooth muscle. In the literature, metoclopramide may be useful in institutions where other D2-antagonists are not available, but otherwise it may not be very efficacious in the management of PONV.

BUTOYROPHENONES

Droperidol is a butyrophenone D2-antagonist and was used as a first-line agent for PONV prophylaxis in low doses in the past. It produces sedation, dysphoria, anxiety, akathisia, and, most notably, QT prolongation. Although instances of sudden cardiac death led to an FDA black box warning in 2001 and a significant decline in its use, the 2020 Cochrane network meta-analysis reported that antiemetic doses of droperidol had a comparable incidence of

### Table 1: D2 Subclass of Antiemetics

<table>
<thead>
<tr>
<th>D2 Subclass</th>
<th>Prototypical Agent</th>
<th>Key Pharmacologic Properties</th>
<th>Important Side Effects</th>
<th>Noteworthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzamides</td>
<td>Amisulpride</td>
<td>Low CNS penetration, low affinity for potassium channels, and cholinergic, adrenergic, and histamine receptors</td>
<td>Mild prolactinemia, low incidence of EPS</td>
<td>FDA approved for use in PONV management</td>
</tr>
<tr>
<td>Butyrophenones</td>
<td>Droperidol</td>
<td>High CNS penetration, high affinity for potassium channels</td>
<td>Sedation, akathisia, QT prolongation</td>
<td>Black box warning, low doses effective in PONV management</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Prochlorperazine</td>
<td>High affinity for cholinergic, adrenergic, and histamine receptors</td>
<td>Sedation, EPS, urinary retention, orthostatic hypotension</td>
<td>Use with caution in elderly patients</td>
</tr>
</tbody>
</table>

QT: refers to the interval between the Q and T points in the ECG  
EPS: Extrapyramidal symptoms  
PONV: Postoperative Nausea and Vomiting  
CNS: Central Nervous System
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over 65 as they can produce central anticholinergic effects (phenothiazines), EPS (benzamides), and tardive dyskinesia, delirium, and NMS (butyrophenones). Also, elderly patients with dementia may have an increased risk of cerebrovascular accident and an increased rate of cognitive decline and mortality with these medications. Similar to adult patients, pediatric patients may experience EPS and QT prolongation with D2-antagonists.

PONV and Clinical Practice Guidelines

PONV contributes to prolonged postanesthesia care unit (PACU) stay, unanticipated hospital admission, and increased health care costs. The fourth consensus guidelines for the management of PONV published in 2020 outline identification of high-risk patients, managing baseline PONV risks, choices for prophylaxis, and rescue treatments of PONV. Two important conclusions from the guidelines should be highlighted here. Prevention of PONV should be considered an integral aspect of anesthesia, and therefore, patients with even one or two risk factors for PONV should receive multimodal PONV prophylaxis. In addition, PONV treatment should consist of an antiemetic from a pharmacologic class that is different from the prophylactic drug initially given, as there is no benefit of redosing ondansetron, despite its common practice.

Various D2-antagonists have been shown to play a beneficial role in both PONV prophylaxis and treatment in the literature. Numerous randomized controlled trials and retrospective database analyses demonstrate that combination regimens of non D2-antagonist antiemetics with various older D2-antagonists such as droperidol, haloperidol, and promethazine, are more effective than either agent alone. However, the use of these agents has declined. To date, amisulpride has been evaluated for the management of PONV in six clinical trials. While five of the trials evaluated monotherapy and demonstrated amisulpride is superior to placebo in the prevention and treatment of PONV, the combination of amisulpride with ondansetron or dexamethasone was more effective than ondansetron or dexamethasone alone in reducing PONV and for rescue PONV treatment.

CONCLUSION

Multimodal PONV prevention and management is critical, especially in enhanced recovery after surgery (ERAS) pathways, patients undergoing ambulatory surgery, and treatment of high-risk patients who have increased acuity and fragility. D2-antagonists can play an effective role given the evidence in the literature, but they also have a wide range of side effects, limiting their use. However, amisulpride is a D2-antagonist with a favorable safety profile, as well as FDA approval for use in the prevention and management of PONV. Therefore, more studies are warranted to compare amisulpride to other single agent antiemetics and its use in combination therapy, as well as cost-benefit analyses.

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The authors have no conflicts of interest.

REFERENCES

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