Novel therapies for nausea and vomiting in advanced illness and supportive cancer care

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***Abstract*:** Nausea and vomiting are common experiences and are often dreaded more than pain. This review discusses blonanserin, mirtazapine, and isopropyl alcohol as antiemetics. Blonanserin, an atypical antipsychotic with a high affinity for dopamine D2 and D3 receptors and serotonin receptor 5-HT2A, has less of a risk of extrapyramidal adverse effects. Transdermal blonanserin, available in Korea, Japan, and China in a small number of trials, has improved nausea in patients not responding to standard antiemetics. Mirtazapine is a noradrenergic and specific serotonergic antidepressant that has been used for multiple symptoms besides depression. There is little evidence that mirtazapine improves anorexia or nausea in advanced cancer but is as effective as olanzapine in reducing chemotherapy-induced nausea and vomiting. Isopropyl alcohol aromatherapy has been successfully used in the emergency department for nausea and vomiting with an onset to benefit more rapidly than standard antiemetics. Isopropyl alcohol prep pads can be used for home-going antiemetic therapy and as a bridge to treating acute nausea until standard antiemetics take effect.

Keywords: blonanserin, isopropyl alcohol, mirtazapine, nausea, vomiting

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Introduction

The prevalence of nausea and vomiting in advanced cancer ranges between 40% and 60%. In a recent guideline, standard antiemetics would include metoclopramide, haloperidol, and the atypical antipsychotics methotrimeprazine and olanzapine based on randomized trials.[1–4] Though frequently used, the serotonin receptor blockers (5HT3 receptor antagonists) have very little proven benefit in treating nausea associated with advanced cancer. To its credit, only tropisetron has been used in one or two randomized trials.

Mechanisms that generate nausea and vomiting are poorly understood. Proposed mechanisms include aberrations in gastric and/or small bowel motor or sensory function, Central Nervous System (CNS) sensory-motor changes leading to impaired gut transit, impaired gastric accommodation, heightened enteric sensitivity, dysautonomia, altered gut-brain communication, and/or psychogenic anxiety.[5] There is a poor correlation between altered gastric motility and the symptoms of nausea and episodes of vomiting.[6] Antiemetic recommendations were based on presumed causes of nausea and vomiting. However, a recent randomized study found that empiric use of haloperidol was as effective as antiemetic choices based on presumed mechanisms.[7]

Three novel medications have recently been found to have antiemetic benefits, either in controlling chronic nausea and vomiting (blonanserin, mirtazapine) or treating acute or breakthrough nausea [isopropyl alcohol (IPA)].

Transdermal blonanserin

Blonanserin is an atypical antipsychotic with a high affinity for dopamine D2 and D3 receptors and serotonin receptor 5-HT2A, approved for the treatment of schizophrenia in Japan, Korea, and China.[8] In a retrospective study involving patients with nausea greater than 3/10 on a numerical rating scale (0 = no nausea, 10 = severe nausea) treated by palliative specialists and having failed to respond to prednisone and prochlorperazine, transdermal blonanserin 20–40 mg daily improved

nausea in 18 of 21 treated patients.[9] A second study suggested that blonanserin increases weight and may be effective in managing cachexia.[10] Cohort studies found that blonanserin also effectively treats or reduces delirium in the intensive care unit and may have multiple palliative benefits.[11–13] A retrospective study of 113 patients with uncontrolled dyspnea at risk for delirium found that transdermal blonanserin 20–40 mg daily appeared to prevent delirium. Blonanserin lowered the risk of delirium (16% *versus* 70%).[14] This needs to be confirmed in randomized trials.

There are several advantages to transdermal blonanserin. Blonanserin has a high affinity for D2 and 5-HT2A receptors and a low affinity for H1, α1, and 5-HT2C receptors, making it is less likely to cause adverse extrapyramidal effects events, such as akathisia.[15–18] Blonanserin's molecular weight (367.5 g per molar) and partition coefficient (Log P of 6) make it ideal for transdermal administration such that if oral administration is not possible, transition to transdermal administration allows for ongoing therapy. An additional benefit is that a switch to transdermal from oral blonanserin further reduces the risk of extrapyramidal adverse effects.[19] Also, the transdermal route reduces risks of drug–drug interactions that would occur within the gastrointestinal tract.[20–22] Blonanserin is not a P-glycoprotein substrate and has a lower risk of prolonging the QTC interval than haloperidol.[23–25] Most neuroleptics reduce seizure threshold by interfering with gamma-aminobutyric acid-induced chloride currents. However, blonanserin uniquely shifts left gamma amino butyric acid concentration-response curves and thus may not reduce seizure thresholds.[26]

Blonanserin is well absorbed by mouth with a bioavailability of 84%, which is the highest among neuroleptics.[8,16] Food increases the maximum plasma concentration if given within 30 min before or after a meal.[27] Oral doses of 8–24 mg daily have the equivalent of D2 receptor occupancy of 40–80 mg transdermal blonanserin.[8] Steady-state D2 receptor occupancy occurs 11 days after starting a 40 mg transdermal patch daily and 7 days after the 80 mg patch.[21] CYP3A4 metabolizes blonanserin in the liver. Drug interactions with midazolam, alfentanil, and verapamil are less likely with transdermal administration.[22]

Twenty-five percent of reported adverse effects of extrapyramidal side effects occur over 52 weeks, including erythema at the transdermal patch site in 41.5% at 52 weeks.[28]

Blonanserin may have a role in treating nausea and vomiting in advanced cancer patients. Still, additional randomized trials using standard antiemetics such as haloperidol and metoclopramide as active controls will be necessary before recommending blonanserin as an antiemetic.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant used for multiple symptoms besides depression.[29–31] Several recent studies have explored the use of mirtazapine as an antiemetic prophylaxis for patients undergoing chemotherapy. As an antiemetic, mirtazapine has successfully treated nausea associated with spinal morphine analgesia, postoperative nausea, functional dyspepsia, intractable nausea and vomiting related to pregnancy, gastroparesis, and nausea as a complication of gastric surgery for obesity.[32–39]

Mirtazapine, nausea, anorexia, and cachexia related to advanced cancer

In a small study of 28 patients with cancer, mirtazapine improved gastric emptying over 2 weeks in the subset of individuals with nausea associated with delayed gastric emptying. Mirtazapine shortened the emptying time from 375 to 128 min.[40] In two single-arm studies involving a small number of patients, mirtazapine 15–30 mg daily improved nausea, depression, sleep, and appetite.[41,42] Twenty percent gained greater than 1 kg of body weight. In another single-arm prospective study involving thirty-nine patients treated with mirtazapine 15 mg daily for 4 weeks, nausea improved on a numerical scale (0 = no nausea, 10 = severe nausea) from an average of 4.6–2.6 ($p < 0.001$). Sleep latency, sleep duration, and sleep quality also improved.[43] A fifth single-arm study involving 30 patients used mirtazapine 7.5 mg daily for 15 days; anorexia as the single outcome. At the beginning of the studies, 62% of patients on a Likert scale had severe anorexia. At the end of the study, none of the participants had severe anorexia, and 23% had restoration of their appetite.[40] In a sixth prospective study of 57 patients with reduced quality of life, 12 of 31 patients with nausea responded to 15 mg daily over 15 days.[44] A retrospective study of 50 patients with advanced cancer reported improved digestive symptoms (nausea, vomiting, and anorexia) in 75% treated

with mirtazapine doses of 1.87–7.5 mg daily.[45] Those with digestive symptoms associated with opioids and chemotherapy responded better to mirtazapine than those with digestive symptoms of unknown cause. A seventh study was a 4-week labeled prospective study of 42 patients with advanced cancer, using the 36-item Short Form Health Survey, the Montgomery-Asbury Depression Rating scale, and the EuroQOL-5 questionnaire to measure multiple outcomes. Of 28 patients with nausea, improvement in nausea and pain was noted on the first day; depression improved by the seventh day. The major side effect was somnolence, which proved transient and improved over time.[43]

Randomized trials provide a different story. The initial trial was an open-labeled crossover, which did not include a placebo. Twenty patients were randomly assigned to 30 or 15 mg of mirtazapine daily for 3 weeks with a 2-week washout. Depression and quality of life improved as measured by the Functional Assessment of Cancer Treatment—General Measure. There was a trend toward improvement in pain by the Memorial Pain Assessment card items and nausea, appetite, anxiety, and insomnia by a numerical scale. In a larger double-blind, placebo-controlled parallel study involving advanced cancer, 120 patients with anorexia (greater than or equal to 4/10 on a numerical rating scale) and cachexia (greater than or equal to 5% weight loss) were randomized to mirtazapine 15 mg or placebo daily over 8 weeks. Appetite improved in both treatment arms with no difference between placebo and mirtazapine. Mirtazapine was noted to reduce depression symptoms but was associated with increased sleepiness.[46] This study demonstrates a significant placebo effect with mirtazapine, which should be considered when assessing prospective single-arm trials. A second study compared mirtazapine with imipramine in a 6-week trial involving patients with advanced cancer. A single symptom scale was used for individual symptoms. There was no placebo arm. Mirtazapine was no better than imipramine in improving nausea and vomiting. There was no improvement in appetite. Anxiety and depression were better with mirtazapine than imipramine.[47] An 8-week randomized trial compared mirtazapine 30 mg daily with megestrol acetate 320 mg daily in 52 patients with advanced cancer. Megestrol acetate was superior to mirtazapine and improved appetite and weight (92% improved on megestrol acetate as opposed to 56% of mirtazapine-treated patients) ($p = 0.007$).

In summary, a prospective single-arm study suggests the benefits of mirtazapine in treating symptoms related to advanced cancer. The few randomized controlled trials centered on gastrointestinal symptoms, particularly nausea and vomiting, are negative. There is a suggestion of a robust placebo effect, which may be responsible for the observed mirtazapine benefits noted in single-arm prospective and retrospective studies.

Chemotherapy-induced nausea and vomiting

Mirtazapine is a promising addition to prophylactic antiemetics and patients undergoing chemotherapy. In a randomized trial of patients treated with either epirubicin plus cyclophosphamide or cisplatin chemotherapy, mirtazapine was added to a combination of aprepitant, a 5HT3 receptor antagonist, and steroids *versus* the three-drug antiemetic regimen alone. Mirtazapine was given on days 2 through 4 at a dose of 15 mg at night. Complete response, defined as no nausea, no vomiting, and no rescue antiemetics, occurred in 78.3% of those treated with mirtazapine *versus* 49% of those treated with a three-drug combination ($p = 0.003$).[48] A second randomized controlled trial compared olanzapine, aprepitant, granisetron, and dexamethasone to mirtazapine, aprepitant, granisetron, and dexamethasone in patients receiving an anthracycline plus cyclophosphamide chemotherapy. Complete response was similar between arms (66.6% with mirtazapine, 63.3% with olanzapine), but mirtazapine had less somnolence and fatigue and less impact on daily life than olanzapine.[49] A retrospective study found that mirtazapine successfully rescues individuals who experience significant nausea and vomiting during their first cycle of chemotherapy.[50] A systematic review of 53 randomized prophylactic antiemetic studies found that the highest probability of complete response occurred when a 5HT3 receptor antagonist, dexamethasone, and either mirtazapine or olanzapine were given in combination with or without an NK1 receptor antagonist like aprepitant.[51]

Mirtazapine has significant benefits as a prophylactic antiemetic. It may be a substitute for olanzapine in those who are intolerant to olanzapine.

Mirtazapine as an antiemetic in general and usefulness in treating symptoms other than depression

Spinal morphine is often used to treat cancer pain and as a postoperative analgesic. Spinal analgesia is associated with significant nausea and vomiting. In a randomized trial of 100 individuals undergoing intrathecal morphine as surgical analgesia, a single 15 mg dose of mirtazapine reduced nausea and vomiting by half compared to a placebo. Fifty-six percent of patients treated with a placebo experienced nausea and vomiting in contrast to 26.5% of mirtazapine-treated patients ($p = 0.0005$).[37] In a similar study, mirtazapine 30 mg as a single dose significantly reduced pruritus from intrathecal morphine (52% of those treated with mirtazapine *versus* 75% of controls experienced pruritus) ($p = 0.0025$).[52]

Mirtazapine plus dexamethasone, compared to dexamethasone alone, reduced postoperative nausea and vomiting for patients undergoing sleeve gastrectomy. Those treated with mirtazapine plus dexamethasone had a 78.6% complete response compared to only 20.7% of those receiving dexamethasone alone ($p < 0.001$).[32] In a similar study, dexamethasone and mirtazapine as single agents were able to reduce postoperative anesthesia shivering compared to controls in patients undergoing gynecological procedures. Clinical shivering occurred in 74% of those on the control arm, whereas it was 16% with mirtazapine and 31% with dexamethasone.[53] Mirtazapine reduces postoperative nausea and vomiting and post-anesthesia shivering. Eighty patients undergoing gynecological surgery were randomized between a placebo and a single dose of mirtazapine 30 mg prior to surgery. Postoperative nausea and vomiting were reduced with mirtazapine. Complete responses were 80% for mirtazapine and 50% for placebo.[38]

Mirtazapine reduces upper gastrointestinal symptoms in patients with functional bowel syndromes.[33,54–57] A randomized trial of patients with dyspepsia enrolled 42 patients, who were treated either with mirtazapine 7.5 mg daily or nortriptyline. Mirtazapine was superior to nortriptyline in reducing epigastric pain, belching, and bloating and improving depression better than nortriptyline.[58]

Mirtazapine has been found to reduce pruritus from multiple causes, including those associated with cancer.[29,59–62] A recent study randomized patients with uremia-related pruritus to gabapentin 100 mg daily and mirtazapine 15 mg daily. Mirtazapine was superior to gabapentin. Patients preferred mirtazapine over gabapentin.[63]

Mirtazapine pharmacology

Mirtazapine is a racemate noradrenergic and specific serotonergic antidepressant with alpha-2 adrenoceptor-blocking properties.[64] Mirtazapine is well absorbed. Adults and the elderly achieve steady-state levels after 4 and 6 days, respectively.[65] Once absorbed, mirtazapine is 85% protein-bound and also binds to erythrocytes.[64,66] Cytochrome CYP2D6 and CYP1A2 metabolize mirtazapine to an 8-hydroxy metabolite and CYP3A4 to an *N*-desmethyl active metabolite and an *N*-oxide inactive metabolite. Mirtazapine directly undergoes glucuronidation; the 8-hydroxy metabolite is also glucuronidated.[67] The active metabolite has the same half-life as mirtazapine which is 20–40 h. Seventy-five percent of mirtazapine is excreted in the urine as metabolites, only 4% as the parent drug.[64]

Mirtazapine is an antagonist at the central alpha-2 adrenergic heteroreceptors, autoreceptors, and a postsynaptic 5HT2 and 5HT3 receptor blocker. As a result, mirtazapine increases noradrenergic neurotransmission and directs serotonin through 5HT1 receptors.[68] Mirtazapine does not block the reuptake of noradrenaline or serotonin. Mirtazapine reduces serotonin side effects such as nausea by blocking 5HT2 and 5HT3 receptors.[69,70] Blocking 5HT2 receptors also improves sleep and 5HT3 receptors nausea. Unlike selective serotonin uptake inhibitors, mirtazapine does not reduce Rapid Eye Movement (REM) sleep but increases sleep duration and quality.[71,72] Onset to antidepressant benefits is quicker than selective serotonin reuptake inhibitors. Mirtazapine improves the receptive relaxation of the stomach by directing serotonin to 5HT1A receptors on nitrergic gastric enteric neurons. This improves gastric accommodation.[73]

Somnolence, the most common side effect associated with mirtazapine, is the most common reason patients stop taking it. Tolerance to somnolence occurs over time. Other side effects include dizziness and fatigue.[74]

Mirtazapine's benefits in treating multiple cancer symptoms need to be explored in randomized trials before it is routinely used for that purpose. It has an

established benefit as a prophylactic antiemetic for patients undergoing chemotherapy. There is evidence that it reduces postoperative nausea, vomiting, and pruritus from multiple causes.

Isopropyl alcohol

Aromatherapy has been used to treat multiple symptoms. According to systematic reviews, aroma therapy has been beneficial in treating pain from dysmenorrhea and is potentially effective in managing pain from labor/childbirth; hypertension; stress, depression, and sleep in hemodialysis patients, stress in healthy adults, perioperative anxiety and sleep and various populations with low-to-moderate confidence in the evidence.[75] IPA has been explored in randomized trials in the management of acute nausea and vomiting in the emergency department and postoperative nausea and vomiting.[76–79] Other aromatherapy agents such as peppermint, ginger, chamomilla, and cardamon are reported for breakthrough nausea and vomiting from chemotherapy; IPA has no published experience.[76,80]

IPA and nausea and vomiting in the emergency department

IPA from 'prep pads' has been used in the emergency department for nausea and vomiting. Beadle *et al.*[81] treated 84 patients to IPA or saline-soaked pads who were admitted to the emergency department with acute nausea and vomiting. Nausea severity in both treatment arms was 6 on a numerical rating scale (0 = no nausea, 10 = severe nausea). At 10 min, IPA-treated patient had improved nausea by three points, while the saline-treated patients had no improvement in nausea. Patients were better satisfied with IPA than saline. Veldhuis *et al.*[82] did a pre-post prospective single-arm study comparing 106 patients with nausea and vomiting. IPA significantly reduced the use of rescue antiemetics (52% pre-IPA and 23% post-IPA) ($p < 0.001$) and reduced overall costs. A parallel randomized trial compared IPA plus ondansetron, IPA plus placebo, and placebo plus ondansetron in 122 patients treated in the emergency department for moderate to severe nausea. The severity of nausea in all three groups was equivalent before treatment (53, 51, and 51 mm on a visual analog scale, respectively, 0 = no nausea, 100 mm severe nausea).[81] At 30 min, both IPA treatment arms had reduced nausea by 30 mm, whereas ondansetron had reduced nausea only by 9 mm. Both IPA arms had lower nausea throughout the study and a greater pain reduction as a side benefit. There was no difference in rescue antiemetics after the study. A third randomized trial compared IPA with a placebo in 118 patients who were admitted to the emergency department with nausea and vomiting. IPA significantly improved nausea within 2 min and was overall significantly better than placebo at 10 min ($p < 0.001$).[83]

A systematic review of IPA in managing nausea and vomiting in the emergency department included all three randomized trials mentioned above. The mean pooled difference in nausea was 2.18 (95% CI: 1.6–2.76) compared to placebo. There was a low risk of bias in each of the studies. Interestingly, there was no difference in the number of individuals who vomited between the IPA and placebo groups, suggesting that IPA was more effective in reducing nausea than preventing vomiting.[84]

IPA in postoperative nausea and vomiting

There is no data to suggest that IPA prevents postoperative nausea and vomiting.[76] Trials consist of point-of-care administration of IPA at the onset of nausea. The timing of administration may be important, and repeat administration is necessary, though this has yet to be extensively explored. It is controversial as to whether IPA in the postoperative setting reduces the need for antiemetics.[79,85–88] Small negative studies have also been published in the postoperative setting.[89,90]

IPA has been compared to promethazine as a rescue antiemetic in 85 patients. All patients received ondansetron as prophylaxis for postoperative nausea and vomiting. IPA was associated with a shorter time to a 50% reduction in nausea than promethazine and an overall reduction in antiemetic requirements.[85] IPA added to ondansetron compared to ondansetron alone in 208 patients undergoing oral/maxillofacial surgery significantly controlled postoperative nausea at 4 and 8 h after surgery.[91]

A systematic review of randomized IPA trials in the postoperative setting found that IPA reduced the requirements for antiemetics (26% with IPA and 39% with placebo) with a number needed to treat to benefit an individual of 8.[92]

A meta-analysis compared IPA with ondansetron for the treatment of nausea and multiple settings. The time to a 50% reduction and nausea favored IPA with a mean difference of 20 min (95% CI: 26–14 min).[93] The outcome of nausea at 30 min favored IPA over ondansetron, and the overall need for rescue antiemetics favored IPA with an odds ratio of 0.6 (95% CI: 0.37–0.95). No adverse events were noted with IPA.[93]

A systematic review of single-arm prospective studies and randomized trials ($N = 13$) included eight blinded randomized trials, eight unblinded randomized trials, and the rest, prospective studies.[80] Of the 13 studies, 7 demonstrated the benefits of IPA in treating nausea. IPA-treated patients responded more quickly than ondansetron; benefits were noted as early as 10 min after administration. IPA in the anesthesia recovery room produced faster relief from nausea than IV ondansetron. Postoperative nausea could be managed at home after discharge with IPA. IPA is superior to promethazine as an antiemetic. The addition of IPA to ondansetron is superior to ondansetron alone.

There are advantages to IPA over standard antiemetics. It is inexpensive, easy to administer, has very few drug adverse effects or drug–drug interactions, and patients can self-administer IPA on an as-needed basis at home if necessary. Some investigators have stated that the benefits of IPA may not be related to IPA but to the deep breathing technique used to administer IPA.[94] Though this is plausible, one randomized study utilized the same breathing technique to administer the placebo and IPA which found IPA superior to placebo.[81] A second proposed mechanism is that olfactory distraction is the reason for benefit. There is a close link between smell and nausea in humans, which makes this proposal plausible.[76]

Conclusion

Blonanserin and mirtazapine may be effective antiemetics in certain clinical circumstances, both could have additional benefits unrelated to nausea and vomiting. Mirtazapine is a better antiemetic for chemotherapy prophylaxis than the treatment of nausea and vomiting in advanced cancer, though further trials are necessary to explore its value in advanced cancer. IPA aromatherapy effectively treats nausea and vomiting in the emergency room and the postoperative setting. IPA could be easily administered while waiting for standard-time antiemetics to take effect and as a rescue for breakthrough nausea.

Declarations

Ethics approval and consent to participate

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Consent for publication

Not applicable.

Author contribution

Mellar P. Davis: Conceptualization; Data curation; Formal analysis; Methodology; Writing—original draft; Writing—review & editing.

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