REVIEW ARTICLE

Nausea and Vomiting After Surgery Under General Anesthesia

An Evidence-Based Review Concerning Risk Assessment, Prevention, and Treatment

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SUMMARY

Background: The German-language recommendations for the management of postoperative nausea and vomiting (PONV) have been revised by an expert committee. Major aspects of this revision are presented here in the form of an evidence-based review article.

Methods: The literature was systematically reviewed with the goal of revising the existing recommendations. New evidence-based recommendations for the management of PONV were developed, approved by consensus, and graded according to the scheme of the Scottish Intercollegiate Guidelines Network (SIGN).

Results: The relevant risk factors for PONV include female sex, nonsmoker status, prior history of PONV, motion sickness, use of opioids during and after surgery, use of inhalational anesthetics and nitrous oxide, and the duration of anesthesia. PONV scoring systems provide a rough assessment of risk that can serve as the basis for a risk-adapted approach. Risk-adapted prophylaxis, however, has not been shown to provide any greater benefit than fixed (combination) prophylaxis, and PONV risk scores have inherent limitations; thus, fixed prophylaxis may be advantageous. Whichever of these two approaches to manage PONV is chosen, high-risk patients must be given multimodal prophylaxis, involving both the avoidance of known risk factors and the application of multiple validated and effective antiemetic interventions. PONV should be treated as soon as it arises, to minimize patient discomfort, the risk of medical complications, and the costs involved.

Conclusion: PONV lowers patient satisfaction but is treatable. The effective, evidence-based measures of preventing and treating it should be implemented in routine practice.

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The incidence of postoperative nausea and vomiting (PONV) after general anesthesia is up to 30% when inhalational anesthetics are used with no prophylaxis. This makes PONV one of the most common complaints following surgery under general anesthesia, together with postoperative pain (1).

As anesthesia is administered approximately 8 million times per year in Germany for surgery, this means that up to 2.4 million patients suffer from PONV every year (e1) if no prophylaxis is provided.

While anesthesia-related mortality and morbidity have fallen dramatically in recent decades, the outcome parameters wellbeing and patient satisfaction are becoming increasingly important (e2). These are considerably affected by PONV (2–4, e3). Financial issues are also significant, as PONV can lead to a substantial prolongation of time in the recovery room with increased costs of personal care (e4) and in pediatric patients PONV is the most common cause of the approximately 1% to 2% of unplanned hospitalizations following outpatient surgery (e5, e6). Despite their rarity, serious complications caused by PONV which are described in case reports, such as aspiration pneumonia, Boerhaave's syndrome, severe subcutaneous emphysema, pneumothorax, rupture of the trachea and loss of vision, provide a warning that this problem is not to be underestimated (e7–e14).

In the German-speaking world, recommendations for preventing and treating PONV were first published in 2007. They were based on searches of the literature up to 2005 and therefore require revision due to new findings (5). Although the recommendations of the Society for Ambulatory Anesthesia (SAMBA), also published in 2007, were based on searches of the literature up to 2006, they require a high level of abstraction because of their claim to international validity. For the German-speaking world, this level of abstraction is difficult to translate directly into treatment recommendations (6).

This review of PONV prevention and treatment is based on a systematic review of the literature with subsequent assessment according to the levels of evidence and grades of recommendations within the framework of expert consensus dating from 2009 (March 30, 2009, Frankfurt am Main, Germany). It can be taken as a

TABLE 1

Levels of evidence and grades of recommendations according to the Scottish Intercollegiate Guidelines Network (SIGN) (e15)

Level of evidence		Grade of recommendation	
	Requirements		Requirements
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias	A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
1 +	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias		
1 –	Meta-analyses, systematic reviews, or RCTs with a high risk of bias	B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal	C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
2 +	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal		
2 –	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal	D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+
3	Non-analytic studies, e.g. case reports, case series		
4	Expert opinion		

basis for incorporation into Standard Operating Procedures (SOPs) in the German-speaking world.

Methods

The recommendations were developed by an expert committee. All participants had many years' clinically-oriented scientific experience in the subject. Before beginning the work, relevant key subjects were presented to the participants for their expert opinions. The subjects were researched using Medline, entering search terms related to each subject in combination with established search algorithms for PONV (including "PONV"; "postoperative" AND ["nausea" OR "vomiting" OR "retching"]). They were then presented and discussed at the plenum, taking the available evidence (published up to and including February 2009) into account. Statements on which agreement had been reached were given a grade of recommendation according to the stipulations of the Scottish Intercollegiate Guidelines Network (SIGN) (*Table 1*; e15). Where there was disagreement, repeat discussions were held using iterative round emails to the participants (modified Delphi technique). In the event of any further disagreement, the disputes were recorded in the manuscript.

PONV risk factors and PONV prognosis systems

The pathogenesis of PONV is still largely unclear. However, in recent years it has been possible to identify a number of risk factors for the occurrence of PONV in adults using multivariate methods (1, 7–11, e16–e22). An overview of the risk factors confirmed by several independent studies is provided in *Table 2*. Results regarding the effect of the type of operation on the risk of PONV are varied, and discussion of them both at the plenum and in the literature therefore includes conflicting opinions (5, 6).

As none of the risk factors listed in *Table 2* alone is sufficiently able to predict PONV, various prognosis systems have been developed. These have a prediction accuracy rate of approximately 70% (1, 7, 12, e18, e23). Due to the heterogeneous nature of the values of the available scores, and given that the predictive value depends on the decision-making criterion in question (number of risk factors) and the prevalence of the disorder (PONV), we refer to further reading in the literature for more detailed description (8, 9). Simplified PONV prognosis systems *(Table 3)* have been shown to have the same prediction ability as more complex PONV prognosis systems (grade B). They are therefore

to be used in preference to more complex systems to assess the risk of PONV, as they are more practicable (grade D; e20, e24).

PONV prevention

An essential part of PONV prevention is the avoidance of confirmed emetogenic factors. Where possible, regional anesthesia should be used, as it is associated with a significantly lower risk of PONV in adults than general anesthesia (grade B; [10, e25]). If general anesthesia is administered, using propofol rather than volatile anesthetics to maintain anesthesia is an effective way of reducing the incidence of PONV (relative risk reduction [RRR] of approximately 19%; grade A; [13, 14]). Not using nitrous oxide is another option for risk reduction (RRR = approximately 12%; grade A; [14, e26]). Avoidance or reduced doses of opioids during (grade B) and after surgery (grade B) also leads to a lower incidence of PONV (1, 13, e27, e28). To this end, non-opioids and/or regional anesthesia, among other options, can be used.

Drug-based PONV prevention

Many different substances belonging to different drug groups are available for drug-based PONV prevention. Today most substances are understood to act as antagonists on specific receptors in the area postrema and on free nerve endings of the vagus nerve. A summary of the most widely-used drugs available in Germany today is provided in *Table 4*.

Adjuvants and non-drug-based PONV prevention

According to the results of a recent meta-analysis, increased inhaled oxygen concentration has no significant effect in preventing PONV (grade A; [e46]). This is also true of ginger and ginger extracts (grade A; [e47]). The panel considered the data on the effect of aromatherapy involving isopropyl alcohol in preventing PONV to be insufficient for providing recommendations (grade D; [e48]).

Studies that have investigated the effect of perioperative fluid replacement on the incidence of PONV are too heterogeneous in terms of both different fluid replacement regimens and results to serve as a valid basis for PONV-prevention recommendations at present (grade D; [e49–e52]).

According to the results of a Cochrane Review, stimulation of acupuncture point P6 on the wrist has been shown to be superior to a placebo (e.g. sham acupuncture) in preventing both nausea (relative risk [RR] 0.72; 95% confidence interval [95% CI] 0.58–0.89) and vomiting (RR 0.71; 95% CI 0.56–0.91) (e53). However, due to study design and its weaknesses regarding treatment blinding, and considerable heterogeneity (e.g. regarding the time of treatment), these conclusions must be interpreted with care (e54). An update of the Cochrane Review on P6 stimulation which included better-designed studies shows again that these treatments achieve a significant reduction in nausea (RR 0.71; 95% CI 0.61–0.83) and vomiting (RR 0.7; 95% CI 0.59–0.83) as compared to a placebo, with minimum side effects in adults and children (grade B; [16]), which ultimately led to a positive overall assessment of this method for PONV prevention in adults and children. Nevertheless, P6 stimulation was awarded a SIGN grade B recommendation in the face of continuing uncertainty regarding its mechanism of action and data which remain very heterogeneous.

TABLE 2

Risk factors for PONV

Group	Risk factor[*1]	Recommendation grade
Patient-dependent	Female sex	B
	History of PONV	B
	Motion sickness	B
	Nonsmoker status	B
Anesthesia-dependent	Volatile anesthetics	A
	Duration of anesthesia (risk increases relatively by approx. 60% every 30 min)	B
	Nitrous oxide	A
Surgery-dependent	Type of operation	D
General	Postoperative opioid administration	A
	Intraoperative opioid administration	A

[*1]The risk factors listed in each group are ordered according to severity (from most to least severe)

Combination prophylaxis and multimodal antiemetic treatment

When deciding on PONV prophylaxis, the following key aspects must be considered:

- For dexamethasone, droperidol and ondansetron, a comparable antiemetic efficacy with a relative risk reduction (RRR) for PONV of approximately 26% has been demonstrated (grade A; [14]).
- Total intravenous anesthesia (TIVA) with propofol instead of volatile anesthetics and air instead of nitrous oxide has been shown to be comparably effective (RRR 31%) (grade A; [14]).
- The effects of a combination of these antiemetic measures (dexamethasone, droperidol, ondansetron and TIVA) are cumulative (grade A; [14]).
- It can be assumed that the results showing a comparable risk reduction for antiemetic measures and the cumulative nature of the efficacy of antiemetic treatment (combinations of antiemetics from different classes) are also valid for the other drug-based measures described in *Table 4* (grade B).
- There is no evidence to date that a specific antiemetic is especially effective for a particular patient profile or a particular operation (grade B; [13]).

TABLE 3

Validated, simplified PONV prognosis systems for adults and children, stating the risk factors involved and calculated incidences of PONV

Prognosis system	Koivuranta et al. (7)	Apfel et al. (1)	Eberhart et al. (12)
Patient population	Adults	Adults	Children
Risk factors	Female sex	Female sex	Age >3 years
	Prior history of PONV	History of PONV History of motion sickness	History of PONV or motion sickness in the child or a first-degree relative
	Prior history of motion sickness		
	Nonsmoker status	Nonsmoker status	Strabismus surgery
	Length of operation >60 min	Expected postoperative administration of opioids	Length of operation >30 min
Calculated incidence of PONV with n risk factors present (sum of the risk factors listed above)			
n	%	%	%
0	17	10	9
1	18	21	10
2	42	39	30
3	54	61	55
4	74	79	70
5	87	Not stated	Not stated

The higher the underlying risk of PONV, the more components from the available antiemetic portfolio are needed to achieve a PONV risk of less than 20% (grade A; [14]). By using a multimodal approach (grade A), it has been possible to achieve a dramatic reduction in the incidence of PONV (less than 10%) and an increase in patient satisfaction, even for high-risk patients with an underlying PONV risk of more than 80% (2, e55).

PONV treatment

When PONV occurs, prompt treatment is indicated, as the likelihood of PONV to persist or to recur is at least 65% (grade A; [11, 17]).

Only $5HT_3$ receptor antagonists have been fully researched for PONV treatment and confirmed as being effective (grade A; [18]). They are, therefore, first-line drugs for treatment of PONV, especially when no prophylaxis has been administered beforehand (grade D). The data available on all the other drug-based and non-drug-based methods described above is less extensive, although dexamethasone (grade A), haloperidol (grade A), dimenhydrinate (grade B) and promethazine (grade C) have been shown to be effective in treating PONV (19, e56, e57).

As those interventions that have proven to be effective (grade A) for treatment of PONV have also been shown to be similarly effective (grade A) for prophylaxis of PONV, there is consensus that the reverse is also true: All interventions for which it has been possible to demonstrate the highest level (grade A) of validated efficacy in preventing PONV, efficacy in treating PONV can also be assumed, and these measures can therefore also be recommended as treatment (grade B). Drug-based measures associated with slow onset of effect (e.g. dexamethasone, scopolamine) should not be used as monotherapy, but only in combination with a fast-acting substance as part of treatment (grade D).

For reasons of practicability, the same doses as those used for prevention are also recommended for treatment (grade D), even though for some substances (e.g. ondansetron) it has been shown that lower doses are also effective for treatment (18).

If PONV occurs despite prophylaxis, the primary recommendation (particularly in the immediate postoperative phase) is to administer a substance from another drug group (grade A; [20, e56, e57]).

In PONV treatment, combination therapy should be considered, as despite treatment the recurrence rate of PONV over the subsequent 24 hours is 35% to 50%, and the combination of dexamethasone plus dolasetron or haloperidol has already been shown to be superior to monotherapy (grade A; [17–19]). A comparable effectiveness as part of combination therapy can also be assumed for other combinations of established antiemetics (grade D).

PONV in children

The incidence of PONV is strongly age-dependent. While children under 3 years of age are rarely affected,

TABLE 4

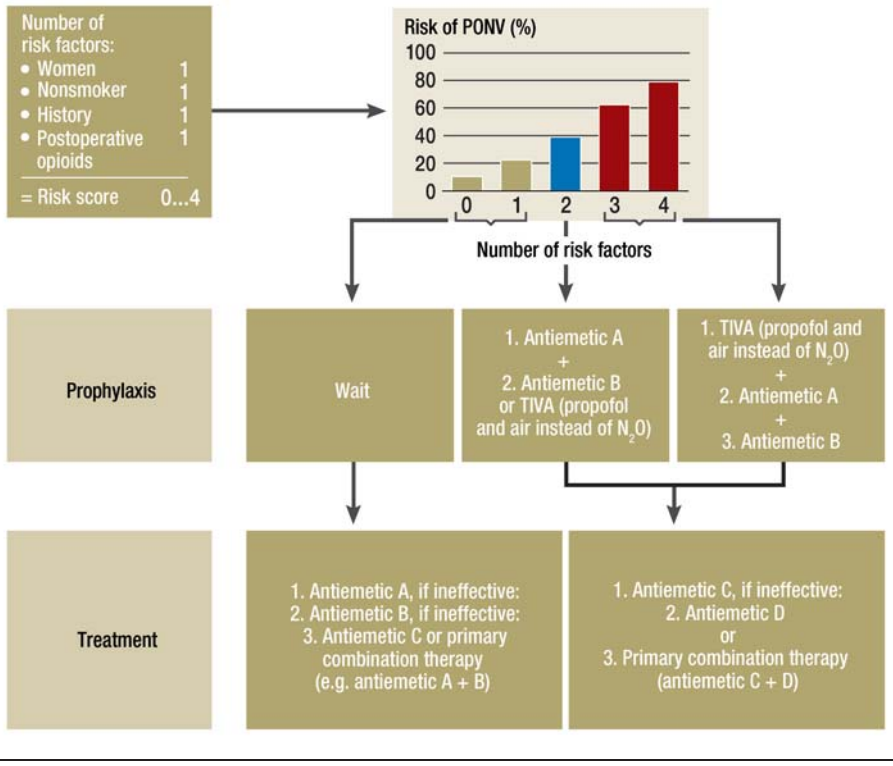
Overview of available antiemetics with well-researched efficacy in preventing PONV

Active substance	Substance group	Dose for adults	Dose for children	Recommendation grade (literature)	Time of application	Recommendation grade (literature)	Adverse effects and contraindications	Remarks
Dexamethasone	Corticosteroids	4–8 mg	0.1–0.15 mg	A (14, 15, e29–e31)	At induction	B (e32)	AEs: increased BG, hypo-/hypertension Rel. CI: diabetes mellitus	Mechanism of action still unclear
Granisetron	Serotonin antagonists (5-HT_3 receptors)	1 mg	0.02 mg/kg	A (14, 15, e33–e36)	End of surgery	B (e37)	AEs: headaches, constipation, raised liver enzymes CI: increased QT interval on ECG	Ongoing: pharmacogenetic studies
Ondansetron		4 mg	0.1 mg/kg					
Palonosetron		0.075 mg	No data					
Tropisetron		2 mg	0.1 mg/kg					
Droperidol	Dopamine antagonists: butyrophenone (D_2 receptors)	0.625–1.25 mg	0.01–0.015 mg/kg	A (14, 15, e33, e38)	End of surgery	A (e38)	AEs: psychomimetic, extrapyramidal disturbance, sedation CIs: Parkinson's disease, increased QT interval	2nd choice for children
Haloperidol		1–2 mg	No data	A (e39, e40)	No effect on efficacy	B (e41)		
Metoclopramide	Dopamine antagonists: benzamide (D_2 receptors)	25–50 mg	0.15 mg/kg	A (11, 15)	30 min prior to end of surgery	D	AEs: extrapyramidal disturbance, hypotension (fast injection)	2nd choice for children
Dimenhydrinate	Histamine antagonists (H_1 receptors)	62 mg	0.5 mg/kg	A (13, e42)	Intraoperatively	D	AE: sedation	
Scopolamine	Anticholinergics (muscarinergic acetylcholine receptors)	1 mg/24 hrs	No data	A (e43)	Evening prior to surgery or at induction	A (e43)	AEs: dizziness, dry mouth, accommodation disturbances	
Aprepitant	Neurokinin antagonists (NK_1 receptors)	40 mg (available only as 80 and 125 mg capsules in Germany)	No data	A (e44, e45)	Together with preoperative medication (currently only available orally)		AEs: headaches, constipation	To be considered for patients at high risk of PONV. Only available to be taken orally. Fosaprepitant (can be used IV) = off-label use

The receptors stated in brackets in the second column are the receptors on which the drug groups indicated in the first line have antiemetic effects. Doses stated are for intravenous administration (except for aprepitant). Side effects listed are the symptoms frequently reported in PONV studies. Level and grade of recommendations according to SIGN criteria; AE: adverse effect; CI: contraindication; BG: blood glucose; ECG: electrocardiogram; IV: intravenous.

Example of algorithm using a risk-adapted, tiered approach

FIGURE 1



from the age of 3 onwards there is a steady increase, peaking between 5 and 9 years of age (e58).

The PONV prognosis systems developed for adults are not suitable for pediatric patients (21). As nausea is difficult to identify in infants and small children, studies of PONV in this patient population are usually limited to the onset of postoperative vomiting (POV). On the basis of risk factors which are well identified in pediatric patients, a simplified prognosis system for children (the Postoperative Vomiting in Children, or POVOC, score, see *Table 3*) has also been developed (12).

Essentially, the same PONV prophylaxis and treatment methods are used as for adults. *Table 4* provides an overview of the dosing for drug-based prevention and treatment. Despite recent disputes regarding the use of dexamethasone, according to the current recommendations of the Task Force for Pediatric Anesthesia of the German Society of Anesthesia administration of 0.15 mg/kg dexamethasone is also considered acceptable in order to prevent PONV (grade A) for adenoidectomies/tonsillectomies (AT/TE) (grade D; [e59, e60]).

Opioid-induced nausea and opioid-induced vomiting

Around 50% of patients who receive opioids as part of patient-controlled analgesia (PCA) suffer from postoperative nausea and vomiting (22).

There are slight differences between opioids in terms of their emetogenic effects:

- Tramadol and buprenorphine are more emetogenic than morphine (grade A; [e61–e71]).
- The emetogenic effects of piritramide, oxycodone and hydromorphone are comparable to those of morphine (grade A; (e72–e76]).
- Fentanyl and remifentanyl are less emetogenic than morphine (grade A; [e77–e84]).

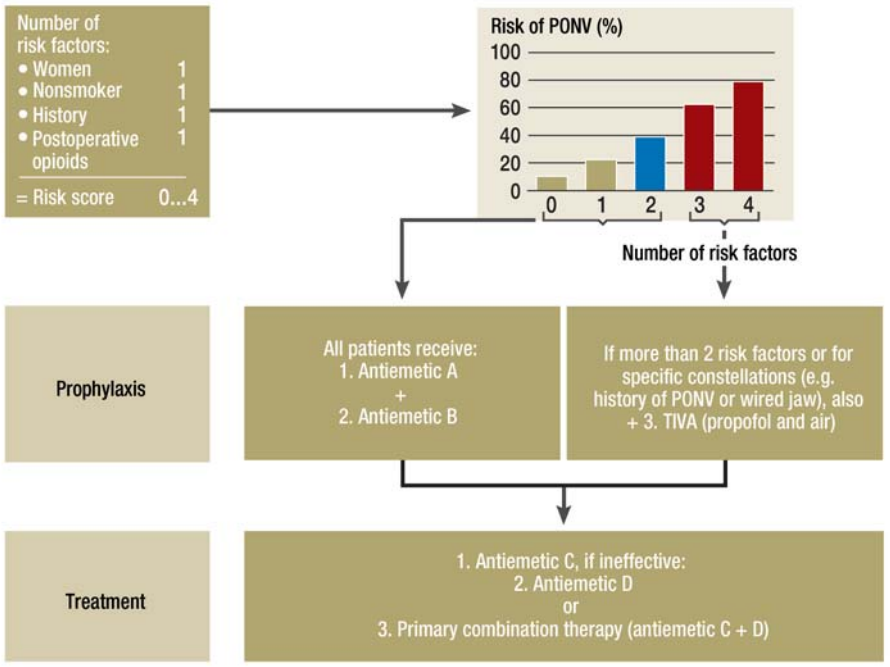
However, these conclusions allow only a limited assessment, using indirect comparison (e.g. comparison of piritramide and fentanyl). Because of the moderate strength of effect, no differential indication exists on opioids to be used perioperatively to reduce PONV (grade D).

Dropiderol (highest daily dose: 4 mg) is the best-researched substance in the prevention and treatment of nausea and vomiting following PCA and therefore is the first choice for both indications (grade A; [22]). A dose of 8 to 12 mg dexamethasone achieves comparably positive results (grade A; [e85]). There are also comparable data available on the efficacy of $5HT_3$ receptor antagonists (grade A; [e86]). Antiemetics with proven efficacy (grade A) for PONV can essentially also be considered effective for the indication "opioid-induced nausea and opioid-induced vomiting" (grade D).

Prevention and treatment algorithms

As the effectiveness of specific algorithms depends substantially on the risk distribution in a particular

FIGURE 2



Example of an algorithm using fixed combination prophylaxis for all patients, extended by an additional intervention if there are several risk factors or specific risk constellations

population, no general recommendations can be given to define a single "best" prevention algorithm (grade B; [23]).

The choice of a risk-adapted approach, for example on the basis of a simplified PONV prognosis system, can be advantageous in saving resources in certain patient populations and can also help to identify patients in need of multiple administration of prophylaxis (grade B). A risk-adapted approach is therefore generally able to reduce an institution's incidence of PONV (grade A; [24, e87]). An example of a risk-adapted algorithm is provided in *Figure 1*.

Inherent limitations regarding risk prediction (grade B) and repeatedly-reported problems in actually implementing a risk-adapted individual approach as part of patient care (grade A) support a risk-independent, standardized approach to prophylaxis (8, 25, e88, e89, e90). The costs of care and the side effect profile of many antiemetics present no obstacle to widespread, liberal use, which means that using a risk-independent algorithm such as a general, fixed dual combination (*Figure 2*) is absolutely justified on the basis of easy implementation. In simulations, the efficacy of this strategy is comparable to a risk-adapted approach, without being undermined by a restrictive dependency on PONV prognosis systems (grade D; [23]). A standardized, risk-independent approach to prophylaxis also has the advantage that standardized—and therefore presumably associated with better compliance—treatment of PONV is also possible.

It is important that both a risk-adapted and a fixed, risk-independent algorithm be modified according to the individual patient's problems (e.g. in patients with wired jaws, major fear due to previous negative experience), i.e. be extended if necessary (grade D; [e91]).

It seems that monitoring *in situ* practicability and preventing insufficient prophylactic administration of antiemetics is more important than the specific choice of a particular algorithm (grade C; [e91]). The data currently available are insufficient to provide a treatment recommendation based on pharmacogenetic considerations (tailored antiemesis) (grade D; [e92]).

The drug-based interventions listed in *Table 4* and researched in many clinical studies exhibit a very good ratio of benefit to adverse effects according to current knowledge. This justifies liberal prophylactic use, as well as multimodal prophylaxis. However, as the side effect profile of antiemetic interventions is variable, the patient-specific benefit/adverse effects ratio must be considered in the light of the patient's individual profile.

The costs of using these antiemetics are varied. Also, purchase prices for different institutions vary to such an extent that any overall pharmacoeconomic examination based on available price levels soon becomes absurd. In the light of this variability and the range of targets for "acceptable PONV incidence," in combination with risk constellations, which vary from institution to institution, a cost assessment can at best be recommended

on the strength of calculations based on the framework parameters of a particular institution (grade D; [23]).

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KEY MESSAGES

- Identify PONV risk factors and use established prognosis systems to assess the risk of PONV, particularly to identify high-risk patients for whom multimodal prophylaxis is indicated.
- Both an individual, strictly risk-dependent algorithm and a risk-independent algorithm associated with fixed antiemetic administration are possible. Risk-independent prophylaxis is therefore preferable in case of doubt, as it is easier to implement.
- There are a number of compatible, thoroughly-evaluated antiemetics available for use in adults and children. When these substances are combined from groups with different active ingredients, their effects are cumulative.
- Total intravenous anesthesia (TIVA) has an anti-PONV effect only if used intraoperatively and cannot be "made up" in the recovery room or on the ward. TIVA should therefore be administered as antiemesis as a high priority, particularly for patients with an above-average risk.
- PONV can be treated as follows: swift administration of drug treatment, as combination therapy if necessary, close monitoring and extension with additional interventions if insufficiently effective.

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REVIEW ARTICLE

Nausea and Vomiting After Surgery Under General Anesthesia

An Evidence-Based Review Concerning Risk Assessment, Prevention, and Treatment

Dirk Rüsch, Leopold H. J. Eberhart, Jan Wallenborn, Peter Kranke

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