Perioperative management of concomitant medication

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Summary

A key component of preoperative evaluation is assessing concomitant medication. Anaesthesiologists must consider potential drug interactions (including attenuation or enhancement of effects) between anaesthetics and the patient's own medication, whilst being aware of the risks involved in perioperative withdrawal of certain substances. With surgery constituting a period of stress for the organism, such changes can threaten a sensitive physiologic equilibrium. For most drugs the ideal perioperative management is poorly understood and so has to be based on an individual risk/benefit assessment. Underpinned by current guidelines and recommendations, the following article reviews the perioperative management of commonly prescribed drugs.

Introduction

A key component of preoperative anaesthesiologic evaluation is the assessment of concomitant medication. An ageing population presenting increasing multimorbidity makes polypharmacy all the more common [1–3]. In 2014, a statistical analysis showed that 36% of those over the age of 65 years were taking 5 or more drugs [4]. Surgical procedures are a stressor for the organism especially of elder and eldest patients, and as such may represent a sustained threat to a labile physiologic equilibrium [5]. It is for this reason that the anaesthesiologist must consider potential drug interactions (including attenuation or enhancement of effects) between drugs used in anaesthetic management and the patient's own medication, whilst being aware of the potential risks involved in the temporary or permanent perioperative withdrawal of certain substances.

For most drugs the ideal perioperative management is poorly understood and so has to be based on an individual and possibly interdisciplinary assessment of risks and benefits [6].

With attention to current research and guidelines, the following digest describes the perioperative management of commonly prescribed drugs. The recommendations are largely underpinned by the current guidelines of the appropriate German and European medical societies [6,7].

Cardiovascular Drugs

Beta-Receptor Blockers

Beta-receptor blockers (beta blockers) are used in the treatment of hypertension, coronary artery disease, heart failure and tachycardic arrhythmias, but also in treating haemorrhagic complications of oesophageal varices, migraine and for the secondary prevention of myocardial infarction [8]. They are one of the most commonly utilised cardiovascular drugs (Table 1).

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As a rule, surgical interventions lead to a physiological stress response, making patients susceptible to prognostically relevant incidents ranging from apoplexy, myocardial infarction and cardiac arrhythmias to life-threatening cardiac events [9]. Beta blockers are effective in reducing not only the heart rate but also the blood pressure, which – amongst other things – attenuates the perioperative myocardial stress response [9, 10]. When overdosed, intraoperative bradycardia and hypotension represent worrisome complications [11].

The administration of perioperative beta blockers is contentious as trials have come to differing results with regard to the influence on morbidity and mortality [10]

- A Cochrane review in 2014 showed a positive effect on the rate of acute myocardial infarction and supraventricular arrhythmias for **non-cardiac surgery**, whilst at the same demonstrating an increase in fatality rate and apoplexy [9].
- With regard to **cardiac surgery**, the administration of beta blockers reduces the rate of ventricular and supraventricular arrhythmias significantly and seems to be advantageous in this population [9].
- In the context of **vascular surgery**, the risk of intraoperative bradycardia and hypotension is increased by administration of beta blockers [11].

Abrupt withdrawal of treatment with beta blockers can lead to a **rebound phenomenon** characterised by tachycardia, cardiac arrhythmias and hypertension. In patients with known coronary artery disease especially, this may in turn cause angina or myocardial infarction, even leading to sudden cardiac death [12,13].

Recommendations for the perioperative period:

- Current long-term treatment with beta blockers should be continued [6,7]
- No unequivocal advice can be provided with regard to perioperative initiation of treatment with a beta blocker; this may be considered:
  - for patients with ≥ 2 cardiac risk factors according to Lee (RCRI*) or an ASA-classification of ≥ III, on whom surgery with a high risk of cardiac complications is to be performed [6,7]
  - for patients with confirmed coronary artery disease and documented exercise induced myocardial ischaemia regardless of the type of surgery [6,7].

  In these cases, a β1-selective agent without intrinsic activity (such as atenolol or bisoprolol) should be preferred [7].
- Initiation of treatment is not recommended when the time span prior to surgery does not allow for dose titration for heart rate and blood pressure, nor for surgical interventions with a low risk of cardiovascular complications [6,7].

Table 1
Perioperative recommendations for commonly administered cardiovascular drugs.

Drug	Perioperative management
Beta blockers	Continue long-term therapy Initiate novel therapy only in the presence of cardiac risk factors in the context of high-risk surgery or for documented exercise induced myocardial ischaemia
ACE inhibitors **AT_1 blockers**	Discontinue for major surgery/sympatholysis/fluid shift Interrupt on the day of surgery if used as an antihypertensive Continue if used in the treatment of heart failure with left ventricular dysfunction
Ca^{2+} antagonists	Continue
Nitrates/molsidomine	Continue
Diuretics	Interrupt on the morning of surgery and continue as soon as possible postoperatively if used for hypertension/heart failure Continue in the presence of hypervolaemia Continue if used in the management of kidney failure
Digitalis	Continue in the presence of non-rapid atrial fibrillation Where appropriate, interrupt when used for heart failure
α_2 agonists	Continue Do not initiate novel therapy in the perioperative period
Statins	Continue long-term treatment Initiate novel treatment 2 weeks prior to surgery for vascular surgical patients

ACE inhibitors and AT_1 blockers

Angiotensin converting enzyme (ACE) inhibitors and angiotensin 1 (AT_1) receptor blockers are used in the treatment of hypertension, heart failure, coronary artery disease, chronic kidney failure and for the reduction of risk of serious cardiac sequelae e.g. following myocardial infarction [14].

ACE inhibitors can improve the haemodynamic situation of patients with heart failure by reducing peripheral vascular resistance. This in turn reduces the left ventricular afterload, increasing cardiac output [15]. The use of ACE inhibitors is therefore recommended in patients suffering any degree of heart failure (NYHA I-IV), especially so in those with left ventricular failure [16,17]. In these

* **Revised Cardiac Risk Index according to Lee:** Heart failure, coronary artery disease (angina and/or previous myocardial infarction), cerebrovascular insufficiency (apoplexy or TIA), diabetes mellitus (insulin dependent), kidney failure (creatinine > 2 mg/dl).

patients, ACE inhibitors reduce overall mortality, whilst also reducing the rate of re-infarction in those suffering heart failure following myocardial infarction [16].

Serious intraoperative hypotension has been reported with perioperative use of ACE inhibitors or AT_1 receptor blockers, especially in those also taking beta blockers and during induction of anaesthesia [7,18].

These hypotensive episodes may be resistant to treatment with conventional vasoconstrictors (e.g. α-sympathomimetics) and instead require the use of **vasopressin analogues** [19,20].

The risks and benefits of perioperative ACE inhibitor use are the subject of debate. Data suggesting continuation during the perioperative period are based on observational studies. Although some research has demonstrated an interrelationship between intraoperative hypotension and preceding ACE inhibiter use, none has shown an increase in cardiovascular complications such as death, apoplexy or myocardial infarction [21]. Observations for AT_1 receptor blockers are analogous, and the availability of evidence is equally limited. As such, the benefits of these drugs, conferred by haemodynamic optimisation, has to be weighed against the risk of intraoperative hypotension. As high-quality evidence is lacking, perioperative management can ultimately only be based on an individual assessment of risks and benefits [22].

Recommendations for the perioperative period:

- For procedures associated with large fluid shifts and for patients with current or intended sympathicolysis (i.e. those treated with beta blockers or receiving peridural anaesthesia) ACE inhibitors and AT_1 blockers should be discontinued [6].
- When ACE inhibitors or AT_1 receptor blockers are used in the treatment of hypertension, stopping that treatment 24 hours prior to surgery may be considered [7].
- When long-term treatment is discontinued preoperatively, it should be reintroduced as soon as possible postoperatively, as 30-day mortality increases otherwise [6, 7].
- For clinically stable patients suffering heart failure with impaired left ventricular function, continued use of ACE inhibitors and AT_1 receptor blockers during non-cardiac surgery, whilst providing close haemodynamic monitoring, is expedient [7].
- For patients suffering heart failure with impaired left ventricular function, introducing novel treatment with an ACE inhibitor or AT_1 receptor blocker at least one week prior to surgery may be considered [7].

Calcium antagonists

Calcium (Ca^{2+}) antagonists can be divided into two different classes based on their effect and indication:

- Dihydropyridines (reference substance: nifedipine) exert their effect primarily through vasodilation in the arterial vascular system. They are used in the treatment of hypertension and stable coronary artery disease [23].
- In contrast, phenylalkylamines (verapamil type) and benzothiazepines (diltiazem type) primarily exert antiarrhythmic effects by reducing heart rate and delaying conduction at the atrioventricular (AV) node. These substances exert a negative inotropic effect, with noticeably less vasodilatory action [21].

The evidence base pertaining to perioperative use of Ca^{2+} antagonists, especially in relation to their influence on prognosis, is limited. Despite an observational study of 1,000 patients undergoing surgical treatment of an aortic aneurysm showing a connection between the use of Ca^{2+} antagonists of the dihydropyridine type and increased mortality [23], overall the risk profile for this class of drug is favourable [21].

Recommendations for the perioperative period:

- Pre-existing long-term treatment with a Ca^{2+} antagonist should be continued perioperatively [6].

Nitrates and Molsidomine

Nitrates and molsidomine are used in the management and prophylaxis of angina attacks [15] and for treatment of acute decompensated heart failure [16].

Nitrates and molsidomine are antianginals which primarily exert their effect on venous capacitance vessels by means of enzymatic (nitrates) or non-enzymatic (molsidomine) release of nitric oxide (NO). Their vasodilatory action on coronary arteries, pulmonary and capacitance vessels results in reduced cardiac preload and thereby improvement of myocardial oxygen balance. Abruptly withdrawing long-term nitrates can result in an increase in angina attacks [15].

Recommendations for the perioperative period:

- Pre-existing long-term treatment with nitrates or molsidomine is continued perioperatively [6,21].

Diuretics

Diuretics are used in the management of hypertension, for heart and kidney failure and in the treatment of pulmonary and peripheral oedema [16,21].

(Loop) diuretics taken during – especially prolonged – preoperative fasting increase the risk of hypovolaemia, which can be associated with metabolic alkalosis [6]. In addition, and in dependence on the mode of action of the various substances, electrolyte imbalances (especially hypokalaemia and hypomagnesaemia) can occur, leading to a risk of perioperative cardiac arrhythmias [21].

Recommendations for the perioperative period:

- When diuretics are used in the management of hypertension and chronic heart failure in clinically stable patients, preoperatively discontinuing the drug for a short time would not be expected to have negative sequelae. Due to the risk of hypovolaemia, they should be discontinued on the day of surgery and reintroduced in an expedient fashion postoperatively [6,21].
- When signs of volume overload are exhibited, treatment should be continued, and the dose adjusted if necessary [7].
- When diuretics are used in the management of advanced chronic kidney failure, they should be continued on the day of surgery [24].
- Electrolyte imbalances, and especially hypokalaemia and hypomagnesaemia, should be treated preoperatively at an appropriate interval prior to surgery. Minor, asymptomatic electrolyte imbalances should not, however, delay emergent surgery [7].

Digitalis

For a long time, digitalis glycosides were used in the management of heart failure for their positive inotropic effect. Meanwhile, they are only recommended for use in that scenario as a reserve drug for patients with reduced left ventricular function who remain symptomatic despite guideline compliant treatment [16]. They are also used for rate control in tachycardic atrial fibrillation, although not as the sole agent for long-term management [25].

Digitalis compounds have a **narrow therapeutic index** and long half-life (1.5 days for digoxin, 7 days for digitoxin) making them **difficult to manage**. The plasma concentration should be at the lower end of the therapeutic range, and drug levels should be monitored 6-monthly and following every change in dose [16]. In hospitalised patients, special attention should be paid to newly introduced potentially nephrotoxic drugs. For patients with prior renal failure taking digoxin, it would seem to be expedient to determine digoxin levels. Attention should also be paid to increased digitalis toxicity in the presence of drug-induced hypokalaemia or hypercalcaemia [15].

Recommendations for the perioperative period:

- When digitalis compounds are used in the management of chronic heart failure, they are usually discontinued preoperatively prior to more major surgery. Due to the long half-life of these compounds, however, the benefit of short-term discontinuation is unclear [6].
- In those patients with non-rapid atrial fibrillation digitalis compounds should not be discontinued preoperatively, as this course of action could cause tachyarrhythmias [6].

α2 agonists

Due to their **effect on the central nervous system**, alpha 2 (α2) agonists such as clonidine are no longer used as preferred agents in the management of hypertension. They are, however, still used in the management of treatment-resistant hypertension or in combination treatment with other drugs [26]. For a number of years now, α2 agonists have also been used in the management of attention deficit hyperactivity disorder [27].

α2 agonists reduce blood pressure mainly by activating peripheral and central α2 adrenoceptors. The decreased release of noradrenaline reduces the sympathetic tone [21]. In addition, a sedating and anxiolytic effect ensues [21].

Whether or not the aforementioned effects of clonidine exhibit a positive effect on the rate of perioperative myocardial ischaemia and mortality, especially in those with coronary artery disease, was most recently the subject of the international POISE-2 trial [28,29]. More than 10,000 patients undergoing non-cardiac surgery were randomised to receive either clonidine or placebo. The mortality rate and the rate of non-fatal myocardial infarction were not reduced by clonidine; however, increased rates of hypotension and non-fatal cardiac arrest were seen [30]. These findings lead to the recommendation in the current ESC/ESA guidelines not to use clonidine in the context of non-cardiac surgery [7].

Abruptly withdrawing long-term treatment with α2 agonists can lead to an excessive activation of the sympathetic nervous system, causing rebound hypertension with hypertensive crisis, tachycardia, agitation and headache. As such, pre-existing treatment should not be withdrawn preoperatively [21].

Recommendations for the perioperative period:

- Pre-existing long-term treatment with α2 agonists can be continued perioperatively
- Based on the findings of the POISE-2 trial initiating novel treatment with an α2 agonist perioperatively cannot be recommended [30].

Statins

Statins (3-hydroxy-3-methyl-coenzyme A reductase inhibitors) are **lipid-lowering drugs** with a proven benefit in primary and secondary prevention of cardiovascular events. They demonstrate anti-inflammatory and stabilising effects on vulnerable vascular plaques and inhibit thrombus formation, and as such can reduce the incidence of perioperative ischaemia, infarction and death in patients with coronary risk factors [6,7,31,32].

Recommendations for the perioperative period:

- Long-term treatment with a statin should be continued perioperatively [6,7].
- Patients undergoing vascular surgery not previously taking a statin should commence prophylactic treatment with a statin at least 2 weeks prior to surgery [6,7].

Anticoagulants and platelet aggregation inhibitors

Perioperative management of anticoagulants and platelet aggregation inhibitors is always subject to risk/benefit assessment taking into account the risk of thromboembolic incidents when treatment is discontinued and the increased risk of bleeding when treatment is continued [6]. This subject is covered extensively in the current **S1-guideline "regional anaesthesia and thromboembolism prophylaxis/anticoagulation"**. As the pertinent recommendations and intervals with respect to neuraxial anaesthesia are expansive and complex, readers are directed to the guideline [33].

Antidiabetics

Oral antidiabetics and GLP-1 receptor agonists

Numerous oral antidiabetics and GLP-1 (glucagon-like peptide) agonists with differing modes of action are available for treatment of diabetes mellitus. Perioperative management is once again dependent on an individual risk/benefit assessment. On the one hand, perioperative stress and post-aggression metabolism put the diabetic at risk of hyperglycaemia with increased susceptibility to infection and osmotic diuresis with hyperosmolality [34]. On the other hand, continuing oral blood glucose lowering drugs puts the patient at risk of hypoglycaemia in the context of perioperative fasting.

Sulfonylureas (e.g. glimepiride) and **glinides** (e.g. repaglinide) stimulate the body's own insulin secretion and can increase the risk of hypoglycaemia when used in the context of perioperative fasting [34].

Due to their mode of action, **glitazones** (e.g. pioglitazone), **α-glucosidase inhibitors** (e.g. acarbose), **gliptins** (e.g. sitagliptin) and **SGLT (sodium dependent glucose transporter)-2 inhibitors** (e.g. dapagliflozin) exhibit a low intrinsic risk of hypoglycaemia [34]. The same is true of the subcutaneously administered **GLP-1 receptor agonists** (e.g. exenatide) [34]. It is worth noting the long duration of action of some members of this class of drug.

On rare occasions, **metformin** can cause lactic acidosis due to cumulation in the presence of kidney failure. The current summary of product characteristics recommends discontinuing metformin 48 hours prior to surgery. However, the risk involved, especially in the context of minor surgical interventions, is very small [35]. Continuing the drug until the evening prior to surgery therefore seems to be justified following an individual risk/benefit assessment [6,34]. However, when intravenous contrast agents are to be used, metformin should be discontinued 24 to 48 hours preoperatively [6,36].

Recommendations for the perioperative period:

- In general, oral antidiabetics should be continued until the evening prior to surgery [34]
- Notwithstanding, following an individual risk/benefit assessment, metformin can be discontinued 24 to 48 hours prior to surgery (particularly when intravenous contrast agents are to be used intraoperatively and for pre-existing kidney failure) [6].

Insulin

Long-acting basal insulins, regular insulin and **short-acting analogues** can be distinguished from one another. Various forms of insulin therapy are used to treat type I and advanced type II diabetes.

- Conventional insulin therapy sees premixed insulin used twice daily, a regimen which requires regular and consistent meals.
- Intensive insulin therapy is based on a basal-bolus regimen: long-acting insulin is used to cover basal requirements, and short-acting insulin is used correctively and at mealtimes.
- Insulin therapy using a pump comes closest to physiologic insulin secretion [34]: the pump is programmed to provide a continuous basal rate of regular insulin or fast-acting analogues (Figure 1).

Basal insulins (e.g. glargine, detemir) have a long duration of action without, however, provoking peaks in plasma-insulin levels. They aim to mimic physiologic basal insulin levels. A missed meal will not immediately cause hypoglycaemia in conjunction with basal insulin use. To avoid ketoacidosis and hyperosmolality, basal insulin therapy should be continued. When patients present a high risk for or positive history of early morning hypoglycaemia, the dose can be reduced by 20 % where appropriate [37]. Other recommendations instead suggest reducing the usual dose by 50% [38]. For brief surgery, insulin therapy using a pump can be continued at the usual basal rate [34,37,39].

The perioperative goal is to maintain blood glucose levels between 140 and 180 mg/dl (7.8 to 10 mmol/l), as more intensive insulin therapy with more aggressive goals leads to an increased risk of hypoglycaemia [37,40].

Type I diabetes

For type I diabetics, insulin is indispensable to life. After just 8 hours of insulin abstention ketoacidosis begins to develop [34]. Basal insulin therapy should be continued; for patients at risk of hypoglycaemia, the dose should be reduced by 20% where appropriate. For patients using an insulin pump, the basal rate should be kept unchanged; alternatively, insulin therapy can be switched to an intravenous regimen on the day of surgery. Regardless of the previous usual regimen, when more extensive surgery is performed insulin therapy should be switched to an intravenous regimen on the day of surgery [34,37,41].

Recommendations for the perioperative period:

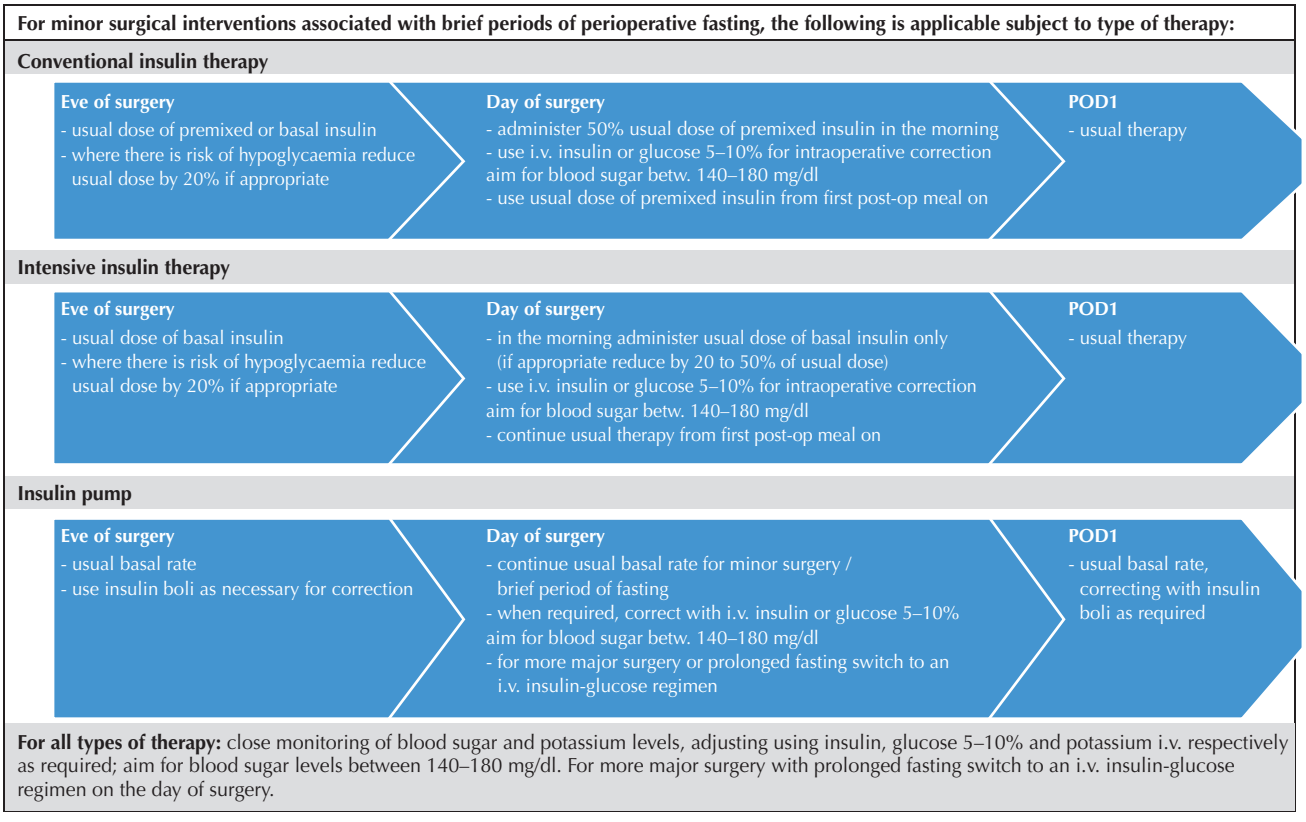
- Administer the usual dose of insulin on the evening prior to surgery [34,41].
- When surgery is brief and an intensive insulin regimen is used, on the morning of surgery basal insulin only should be administered [6,34]. Where there is a risk of hypoglycaemia the dose can be reduced by 20% [37,39].
- When surgery is brief and conventional insulin therapy is used, on the morning of surgery the usual dose should be reduced by 50% and administered in the form of premixed insulin [6].
- Insulin therapy using a pump can be continued for brief surgery. For more significant surgery of longer duration insulin therapy should be switched to an intensive or intravenous regimen [34].
- For more extensive surgery with a probable extended period of inadequate oral ingestion, therapy should be switched to an intravenous insulin-glucose regimen [34,37,41].
- Close monitoring of blood glucose and potassium levels during the perioperative period is vital [6,34].
- As a general rule, hyperglycaemia should be treated with insulin and hypoglycaemia should be treated with glucose (intravenously for the period of perioperative fasting).

Psychotropics

Psychotropics are commonly prescribed for psychosis, depression, epilepsy and sleep disturbance [15]. Long-term treatment is usually not discontinued perioperatively [6]. However, miscellaneous side-effects and drug interactions need to be taken into account with perioperative psychotropics (Table 2).

Tricyclic antidepressants are classic drugs used for the treatment of depression and as a component of multimodal pain management. They inhibit the reuptake of dopamine, noradrenaline and serotonin in the central nervous system (CNS) and peripheral tissues, increasing the level of these transmitters in the synaptic gap [6]. Due to diverse selective effects of these substances, and their partly inhibitory effects on a number of other receptors (e.g. histamine, serotonin, noradrenalin receptors) they offer up a manifold side-effect profile [15]:

Figure 1



Management of insulin-dependent diabetics. **i.v.:** intravenous; **betw.:** between; **POD:** post-operative day.

- A prolonged QT interval may become apparent in the ECG [15].
- The effect of direct sympathomimetics is increased, whilst that of indirect sympathomimetics is decreased [42]. This should be taken into account when using local anaesthetics with the addition of adrenaline [6].
- The effect of hypnotics, opioids and inhaled anaesthetics is potentiated [6,42].
- Tricyclic antidepressants are metabolised via the CYP_{450} system (cytochrome P_{450}), leading to interactions with other substances which are metabolised in the same way [42].

Serotonin reuptake inhibitors (SSRI) and **serotonin-noradrenaline reuptake inhibitors (SNRI)** inhibit the reuptake of serotonin and/or noradrenaline in the synaptic gap [15].

- Discontinuing these drugs can cause withdrawal symptoms [6].
- Concurrent administration of other drugs which inhibit the reuptake of serotonin or exhibit serotomimetic actions (e.g. pethidine, pentazocine, tramadol, MAO inhibitors) can cause a **serotonin syndrome** with grave consequences (hyperthermia, vegetative instability and impaired consciousness ranging to coma) [6,15].
- Metabolism via the CYP_{450} system leads to interactions with other substances which also undergo metabolism via this enzymatic system [42].

Monoamine oxidase (MAO) inhibitors also increase the concentration of monoamines in the synaptic gap. Two subclasses can be distinguished: MAO-A is expressed ubiquitously, whilst MAO-B is predominantly expressed in the CNS. Depending on the agent, inhibition is selective or non-selective and reversible or non-reversible. Whilst first generation drugs (e.g. tranylcypromine) are non-selective and irreversible in their action on MAO-A and MAO-B, second generation drugs are selective and irreversible (clorgiline affecting MAO-A, deprenyl affecting MAO-B). Third generation drugs are both selective and reversible (e.g. moclobemide affecting MAO-A) [6]. Treatment with MAO inhibitors causes a wide array of pharmacological interactions; only those which are most important from an anaesthetist's viewpoint are listed here [15]:

- There have been reports of the release of noradrenaline by indirect sympathomimetics causing hypertensive crises which were difficult to manage [6].
- An excitatory reaction due to excessive serotonergic activity (type I serotonin syndrome) can be caused by administration of pethidine or tramadol [6,42].
- The inhibition of CYP_{450} can prolong the duration of action of opioids [42].

The seriousness of these incidents used to mean that withdrawing these drugs prior to elective surgery was obligatory, especially when irreversible, non-selective MAO inhibitors had been used.

Practical recommendations:

- Today, so long as the absolute contraindications to the adminis-

Table 2

Management of psychotropics in the context of elective surgery (adapted from [42]).

Risks	TCA	SSRI SNRI	MAOI	Lithium	Neuroleptics	Methylphenidate
Direct effects	Anti-cholinergic symptoms Cardiac arrhythmias	Serotonergic symptoms	None	Cardiac arrhythmias CNS symptoms GIT symptoms	Anti-cholinergic symptoms Extra-pyramidal motor symptoms Cardiac arrhythmias	Cardiac arrhythmias Tachycardia
Interactions	CYP_{450} system Hypnotics Sympathomimetics	CYP_{450} system Benzodiazepines Serotonergics	Catecholamines Serotonergics Opioids CYP_{450} system	ACE-I Diuretics NSAID Muscle relaxants	ACE-I Antacids	MAOI $\alpha 2$ agonists
Observe	ECG: QT interval	ECG: QT interval	Absolute CI for pethidine tramadol, indirect sympathomimetics	Narrow therapeutic index: determine levels	ECG: QT interval	Depletion of endogenous catecholamine stores possible
Discontinue	No	No	Reversible MAOI: No Irreversible MAOI: switch prior to surgery	Minor surgery: No More major surgery: 72 h prior to surgery	No	Where appropriate interrupt on the morning of surgery
Withdrawal symptoms on discontinuing	Yes	Yes	Reversible MAOI: No Irreversible MAOI: Yes	No	Yes	No

TCA: Tricyclic antidepressants; **SSRI:** selective serotonin reuptake inhibitors; **SNRI:** selective serotonin-noradrenaline reuptake inhibitors; **MAOI:** monoamine oxidase inhibitors; **CNS:** central nervous system; **GIT:** gastrointestinal tract; **ACE-I:** angiotensin converting enzyme inhibitors; **NSAID:** non-steroidal anti-inflammatory drugs; **CI:** contraindication.

tration of pethidine and tramadol are observed and indirect sympathomimetics (e.g. ephedrine) are not used, discontinuing MAO inhibitors is not seen as a requirement [6,42].
- For elective surgery, 2 weeks prior to surgery irreversible MAO inhibitors should be exchanged for reversible MAO inhibitors in collaboration with the patient's psychiatrist [6].
- To date, there are no reports of perioperative complications in patients taking reversible MAO inhibitors [6].

Lithium is predominantly used in the treatment of bipolar and affective disorders. Lithium is eliminated renally. Due to the narrow therapeutic index, close monitoring of lithium levels is recommended [6]. In a perioperative setting, it is pertinent to pay attention to possible worsening of renal function, e.g. in conjunction with the administration of drugs with nephrotoxic side-effects [42]. Drug interactions which are relevant from an anaesthetic point of view cause
- prolonged neuromuscular blockade,
- reduced anaesthetic requirements due to inhibitory effects on central neurotransmitter systems and
- an augmentation of cardiac excitation and conduction [42].

Practical recommendations:
- If lithium therapy is continued perioperatively, e.g. in the setting of minor surgery, levels should be monitored closely [6].
- When therapy is discontinued, withdrawal symptoms are not to be expected. As lithium toxicity can cause life-threatening complications, there is debate surrounding withdrawing the drug 72 hours prior to surgery [6,42].

Neuroleptics are a heterogenous group of drugs with antipsychotic and in some cases sedating effects. They are used in the treatment of schizophrenic psychoses and the psychotic symptoms of affective and bipolar disorders [42]. Because there is a risk of renewed psychotic symptoms, withdrawing these drugs perioperatively is not justified [6,42]. With regard to anaesthetics the potential sedative effect, possible QT prolongation and an α1-adrenergic antagonist effect should be taken into account [42].

Antiepileptics should be continued perioperatively. These patients may require higher doses of opioids and neuromuscular blocking agents [6].

Methylphenidate is an amphetamine derivate, used mainly in the treatment of attention deficit hyperactivity disorder [43]. Amphetamines exert an indirect sympathomimetic effect. Chronic use can cause a depletion of endogenous catecholamines [15]. The reduced sympathetic counterregulation can lead to bradycardia and hypotension in the context of induction of anaesthesia. There have been reports of serious incidents [44]. The recovery of intraneuronal catecholamines takes days to weeks, so that discontinuing these drugs shortly prior to surgery will not protect from the aforementioned complications [44].

Practical recommendation:
- Long-term treatment with methylphenidate can be continued until the day of surgery [6].

Antiparkinson drugs

Parkinson's disease is treated using
- Levodopa (L-dopa)
- Dopamine agonists
- MAO-B inhibitors
- Cathechol-O-Methyltransferase (COMT) inhibitors
- N-Methyl-D-Aspartate (NMDA) antagonists and
- Anticholinergics.

The aim of these agents is to increase the concentration or effect of **dopamine** in the brain, either directly (L-Dopa), indirectly (e.g. bromocriptine) or by inhibiting degradation (e.g. selegiline). Permanently or temporarily discontinuing these drugs can cause complications ranging from muscle rigidity to Parkinson's crisis with swallowing difficulties and respiratory impairment [45].

Practical recommendations:
- Antiparkinson drugs should be administered on the morning of surgery and continued immediately postoperatively [6].
- If peroral administration will not be possible postoperatively, therapy can be switched to a transdermal system preoperatively in collaboration with the patient's neurologist [6].
- In the context of prolonged surgical interventions or where there is the possibility of insufficient deglutition postoperatively, intraoperative placement of a gastric tube is expedient. The decision to provide postoperative monitoring on an intensive care unit should be taken liberally [46].
- Dopamine antagonists (e.g. metoclopramide) and drugs which can cause extrapyramidal side-effects (e.g. droperidol, HT_3 antagonists) should be avoided in these patients [6].

Corticosteroids

Long-term treatment with corticosteroids can cause disruption to the hypothalamic-pituitary-adrenal axis leading to **secondary adrenal insufficiency** [47]. Inadequate cortisol production e.g. in the context of the perioperative stress response can lead to vasodilation, hypotension and shock, but also to impaired consciousness [47].

As a matter of principle, all patients who have received steroids for ≥ 5 days, regardless of dose and route, are at risk of insufficient endogenous cortisol production [48]. As such, long-term treatment should not be interrupted in the perioperative period [6,47,49].

Knowing which patients will benefit from an **additional perioperative dose**

in the context of surgical interventions is a question which cannot be answered definitively. On the one hand, current German guidelines based on expert opinion recommend a stress dose for any patient who has received steroids for at least 5 days, regardless of dose and route [6]. On the other hand, there is evidence showing that a stress dose confers no advantage or increased haemodynamic stability in those in whom usual long-term steroid therapy has been continued [50–53]. As such, steroids should not be used indiscriminately in the perioperative setting, as they may lead not only to hyperglycaemia at higher doses, but also cause other known side effects, such as an increased risk of wound infection and delayed wound healing [54,55]. Current reviews have noted that small sample sizes and insufficient quality of evidence in pertinent trials mean that routine administration of a stress dose can neither be advocated nor rejected [53,56].

The risk of adrenal insufficiency is to be considered slight in those patients taking any dose of steroids for less than three weeks, taking less than prednisolone 5 mg per day or less than prednisolone 10 mg every two days. Routine substitution of a stress dose does not seem to be necessary in these patients, so long as they do not display signs of adrenal insufficiency [47]. The decision for or against administration of a stress dose should not only take the individual risk of adrenal insufficiency into account, but also make allowances for the magnitude and complexity of the surgical intervention and resulting stress response [53].

Practical recommendations:

- Long-term treatment with steroids should be continued on the day of surgery, independent of dose, duration and route of current therapy [6].
- Where a stress dose is required, on the basis of expert opinion, the following approach is recommended [6]:
  - Minor surgical interventions (e.g. herniotomy, thyroid surgery): hydrocortisone 25 mg when surgery commences
  - Medium interventions (e.g. abdominal surgery): hydrocortisone 100 mg over 24 hours, continuation of the usual long-term steroid therapy on the following day.
  - Major surgical interventions: hydrocortisone 100 mg over 24 hours, 50 mg over 24 hours the following day, and hydrocortisone 25 mg (oral administration admissible) on the third postoperative day [6].

Bronchodilators

In the main, antiobstructive drugs are used in the treatment of bronchial asthma and COPD (chronic obstructive pulmonary disease). These patients have been shown to have an increased perioperative risk of complications such as bronchospasm, hypoxia and postoperative respiratory failure [57]. Depending on the severity of the disease, short and fast-acting or long-acting **β2-mimetics** in the form of inhaled bronchodilators, **anticholinergics** and – depending on the course of the disease – inhaled or oral **corticosteroids** are used in disease management. Treatment slows progression of the disease and prevents exacerbations.

Practical recommendation:

- Pulmonary antiobstructive drugs should be continued in the perioperative period [57].

Opioids

General aspects

Patients on long-term opioids, whether for management of a chronic pain syndrome or in those with addictive disorders with or without opioid substitution therapy, often pose a particular challenge for anaesthesiologists. Regardless of the reasoning behind long-term opioid use, **opioid tolerance** ensues, and ever larger doses are required to produce the same effect [15]. Discontinuing these drugs rapidly can cause **opioid withdrawal syndrome** [15]. Both long-term opioids and opioid substitution therapy should be continued in the perioperative period. They represent basal therapy and prevent withdrawal. Treatment may need to be expanded to meet the requirement for postoperative analgesia [58].

In principal, all forms of anaesthetic management can be used in these patients; regional anaesthesia alone or in combination with general anaesthesia should be preferred, however [59–62]. Remifentanil, a very short-acting opioid, can induce a withdrawal syndrome in opioid tolerant patients and should therefore be avoided [58].

Buprenorphine

Buprenorphine is used in the treatment of pain syndromes and for substitution. Due to its partial agonist effect with a high affinity for μ-receptors, its perioperative use is mired in uncertainty. When high doses of buprenorphine are used, there is a risk the action of pure μ-agonists may be impeded [58].

- In the context of more significant surgical interventions with an expected high level of perioperative pain, preoperative conversion to a pure μ-agonist is to be recommended [58,61].
- For more minor surgery, treatment with buprenorphine can be continued; opioid and analgesic requirement may, however, be increased in these patients [61].

Transdermal systems

In the context of more major surgery, it is necessary to take changes in cutaneous circulation and the ensuing uncertain resorption of transdermal drugs into account.

- With minor surgical interventions, transdermal systems can be left in place, providing basal therapy [58].
- For more major surgery, the removal of the transdermal patch following induction of anaesthesia is to be recommended. Basal requirements should then be covered by the intravenous route, possibly switching to peroral administration of pure μ-agonists in the course of the postoperative period [58].

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