Psychotropic Drugs and the Perioperative Period: A Proposal for a Guideline in Elective Surgery

FRITS J. HUYSE, M.D., PH.D., DAAN J. TOUW, PHARM.D., PH.D.
ROB STRACK VAN SCHIJNDEL, M.D., JAAP J. DE LANGE, M.D., PH.D.
JORIS P.J. SLAETS, M.D., PH.D.

Evidence-based guidelines for the perioperative management of psychotropic drugs are lacking. The level of evidence is low and is based on case reports, open trials, and non-systematic reviews. However, the interactions and effects mentioned indicate that patients who use psychotropics and require surgery have an enhanced perioperative risk. A group of clinicians from several clinical disciplines determined which risks should be considered in an integrated preoperative assessment, as well as how psychotropics might interfere with these risks. The risks that should be considered in the perioperative period are the extent of the surgery, the patient's physical state, anesthesia, the direct and indirect (Phase I and II) effects of psychotropics, risk of withdrawal symptoms, and risk of psychiatric recurrence or relapse. Because of new drug developments, the risk of interactions increases. The literature has not provided articles that systematically address these risks. On the basis of a systematic analysis of the available literature guided by the formulated perioperative risks, a proposal for the perioperative management of psychotropics was formulated. Patients who use lithium, monoamine oxidase inhibitors, tricyclics, and clozepine have serious drug–drug interactions, with increased physical risks, including withdrawal, and therefore qualify for American Society of Anesthesiologists (ASA) Classification 3. From the perspective of the physical risk, they require discontinuation. However, from the perspective of the risk of withdrawal and psychiatric relapse and recurrence, these patients deserve intensive, integrated anesthetic/psychiatric management. For patients on selective serotonin reuptake inhibitors (SSRIs) who are mentally and physical stable (ASA Classification 2), the risk of withdrawal seems to justify their continuation. Yet, patients on SSRIs with higher physical or psychiatric risks should be seen in consultation. Both the physical and psychiatric risks of patients who use antipsychotics and other antidepressants should be regarded as enhanced. From a physical perspective, they qualify for ASA Classification 2. From the perspective of withdrawal and psychiatric recurrence or relapse, they should be seen by (their) psychiatrists. Preoperative assessment clinics offer the opportunity to assess and evaluate these risks in order to deliver patient-tailored integrated care. Authors propose a model for quality management.

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Received December 23, 2003; revised April 16, 2004; January 5, 2005; accepted February 4, 2005. From the Dept. of General Internal Medicine, University Medical Center, Groningen, the Netherlands; the Depts. of Intensive Care and Anesthesiology, University Medical Center, Vrije Universiteit, Amsterdam; and Apotheek Haagse Ziekenhuizen, The Hague, The Netherlands. Send correspondence and reprint requests to Dr. Huyse, Dept. of Internal Medicine, Hanzeplein 1, PO Box 30.001, 9700RB Groningen, the Netherlands; e-mail: f.j.huijse@int.azg.nl

In 1988, a call was made for a more preventive and structured approach to the preoperative assessment and pre- and postoperative medical evaluation of surgical patients.[1] The clinical objective for preoperative assessment was a move toward evidence-based guidelines. This should lead to reduction of morbidity and mortality and enhancement of quality of care. Also, it should result in a reduction of

costs by avoiding unnecessary procedures. It has guided the development of pre-assessment clinics, where surgical patients are procedurally evaluated before elective surgery. This offers an opportunity to change from ad-hoc psychiatric consultations in inpatients admitted for surgery, where the anesthesiologist or surgeon perceives a specific surgical problem related to psychotropic drug use, to a more integrated approach in a pre-assessment clinic; this would include guidelines for psychotropic drug-management in the perioperative period. Their focus should be on risk-management to prevent perioperative mortality, physical morbidity, withdrawal problems, and acute or long-term relapse of psychiatric morbidity, thereby preventing last-minute cancellation of surgery.

Such guidelines should include indications for interdisciplinary consultations. The need for a systematic approach toward perioperative psychotropic drug-management was first addressed in a study assessing the use of psychotropic drugs in a preoperative-assessment clinic population. Three hundred surveys were distributed, with a response rate of 53%. Of those who responded, 43% used psychotropic drugs. Of these patients, 35% used antidepressants; 34%, benzodiazepines; 19%, combinations of these and other psychotropics, such as antipsychotics, lithium, and over-the-counter drugs.[2]

A survey (response rate: 75%) among 150 United States anesthesiology programs, assessing the current practice of their perioperative handling of chronic medications, revealed a large inter-practice variation.[3] The average rates for discontinuation of the most prevalent types of medication were the following: aspirin: 82%, ibuprofen: 77%, monoamine-oxidase inhibitors (MAOIs): 51%, diuretics: 38%, tricyclics: 9%, and oral contraceptives, 4%. In a recent series of articles in *Drugs and Therapeutics Bulletin*, which is a U.K. independent review for doctors and pharmacists from the consumers' association, it is stated that there are few published data to formulate a guideline for chronic drug-management in the perioperative period.[4] Therefore, they conclude that physicians generally rely on their own experience, which explains the large inter-practice variation.[3] The best evidence for the development of clinical guidelines is from randomized, controlled trials. Yet, the area of drug–drug interactions is not an area for such studies because the number of combinations of drugs is too high, and studies could easily become unethical. This is an area where the patient is the "guinea pig," and the clinician gains knowledge by being a good observer of clinical evidence of these interactions. On the other hand, possible hazards may be assessed by clinical reasoning, combining different pieces of available information.[5] Because the risks involved come from intensivistic, anesthesiological, pharmacological, geriatric, and psychiatric perspectives, in this article, medical specialists who represent these perspectives will combine available evidence and clinical reasoning to formulate a proposal for perioperative psychotropic drug-management in elective surgery. For the above-mentioned reasons, the evidence might be thin; however, the primary objective is to provide a framework for integrating clinical reasoning and a model for integrated risk-management that can be part of pre-assessment quality management.

METHOD

Through clinical reasoning, the authors formulated a series of risks to be considered in patients who use psychotropics and apply for elective surgery. These risks are described under Decisions to Be Made, in the Results section. The literature is reviewed to evaluate the empirical evidence available against these formulated risks. This is described under Available Evidence, also in the Results section. A MEDLINE search combining "anesthesia" or "preoperative care" or "perioperative care" and "mental disorders" or "psychotropic drugs," "antipsychotic agents," "antidepressant agents," or "serotonin reuptake inhibitors," "monoamine oxidase inhibitors," or "lithium" did reveal that evidence on the level of metaanalysis, randomized clinical trials, or practice guidelines was not available, except for the guideline suggested by *Drugs and Therapeutics Bulletin*.[4] The main evidence was on the level of non-systematic reviews, open trials, and case reports assessing selective aspects of the earlier-formulated physical and psychiatric risks. As a result of clinical reasoning and available evidence, we make a proposal for drug-management for psychotropics. The following drugs have been evaluated: lithium, MAOIs, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), other antidepressants, classic antipsychotics, second-generation antipsychotics, and clozapine. The risks of benzodiazepine use for excess sedation or withdrawal related to perioperative use are not discussed because this is part of day-to-day anesthetic practice,[6] nor are specific perioperative risks discussed in patients with substance abuse.

RESULTS

Decisions to be Made

As seen in Table 1, there are two main risks to be dealt with in patients selected for elective surgery, who use psy-

chotropic drugs. The primary risk of psychotropic use to be considered is excess morbidity and mortality through physical interferences. The physical risks of surgery include the extent of the surgery, the specific disease/handicap that requires surgery, physical comorbidity, and type of anesthesia. Psychotropic drug use should be seen as a physical comorbidity with risks of interaction and physical withdrawal. Thereby, it leads to excess physical morbidity and mortality. The second risk concerns the impact of discontinuation of psychotropic drugs on the psychological functioning of patients with existing psychiatric morbidity. This includes the risks of psychological withdrawal and psychiatric recurrence or relapse.

Extent of Surgery The first risk to be taken into account is the type and extent of surgery, its stress-inducing effects, and its related impact on the metabolism of, for instance, cortisol, cathecholamines, and cytokines.[7] A classification for the level of stress-induction by the different surgical procedures has been proposed. Procedures associated with moderate-to-severe stress, such as open abdominal surgery, increase heart rate and plasma levels of cortisol, as well as epinephrine and norepinephrine. Other procedures, which do not induce such changes, are considered as minimally stress-inducing.[7] The level of stress-induction for the size of surgery is operationalized as follows: 1) moderate (e.g., appendectomy, mastectomy, TUR); 2) large (e.g., laparotomy, bowel-resection, cholecystectomy with choledochotomy, peripheral-vascular surgery, or major amputation); and 3) very large (e.g., aorta surgery, abdomino-perineal resection, pancreatic- or liver resections, esophago-gastrectomy).[7] In the Practice Advisory for Pre-anesthesia Evaluation by the American Society of Anesthesiologists, a comparable classification of surgical invasiveness is proposed (low, moderate, or high) without further specification.[8] Another measure for the impact of surgery is the direct operative mortality. However, in elective surgery, the direct operative mortality is very low and therefore is not a discriminative factor.

Physical Status The risk of the patient's physical status for the outcome of surgery comprises two components: 1) the status related to the disease/handicap indicated for surgery; and 2) the status related to the patient's comorbidity. The impact of the disease/handicap is reflected in the direct operative mortality. The risk of the comorbidity is classified in the generally accepted classification of the American Society of Anesthesiologists; the ASA classification.[9] Its main purpose is to differentiate among patients without comorbidity, those with light-to-moderate system

TABLE 1. Risks to be Considered in Patients Receiving Psychotropics in the Perioperative Period

Extent and Type of Surgery	Local Infiltration for Excisions Versus Larger Surgery
Effects on pharmacokinetics Stress-induction Oral or abdominal surgery Need for post-operative ventilation	
Physical status, including substance use disorders	**ASA classification[9]** I. Healthy patient II. Mild systemic disease III. Severe systemic disease with functional limitations IV. Severe systemic disease, constant threat to life V. Moribund, unlikely to survive 24 hours
Anesthesia	**See Table 2**
Direct effects	According to Dawson et al.[15]
Drug interactions	Beneficial Possible Of note Hazardous Results in the need to discontinue
Access to the body	Oral, suppository, intramuscular, intravenous
IV-IM change and alternative drugs	Yes/No/Irrelevant Most evidence available with benzodiazepines and haloperidol
Psychiatric	
Withdrawal	Results in the need for psychiatric consultation
Risk of psychiatric relapse or recurrence	Results in the need for psychiatric consultation

problems with no functional impairment, and those with more serious system problems, with functional restrictions. Among the patients with physical comorbidity, there are two specific groups who are of interest from the perspective of psychotropic drug use: First, there are those patients who have, because of their physical morbidity, diminished functional capacity of organs that are crucial for the metabolism of drugs and their excretion; the kidney and the liver.[10–12] The same is true for frail elderly patients, because of reduced compensational capacity of several organ systems.[13] These are patients at risk for delirium. Such risks should have been taken into account at prescription. The second group comprises addicted patients. These patients might underreport their physical state or might not report their addiction and, as a consequence, suffer withdrawal, including delirium, and may have complex behavioral problems that interferes with medical care. In this group, effects of anesthetics might be influenced by enzyme-induction.[12,14] Furthermore, these patients are at risk for organ-failure, such as in cirrhosis.

Anesthesia The third factor influencing perioperative morbidity and mortality is related to anesthesia, itself, and the increase in this risk due to the combination of anesthetic drugs with other drugs, such as psychotropics. Modern anesthesia is flexible. This flexibility offers an opportunity to reduce or avoid drug–drug interactions. Before the decision on type of anesthesia, direct and indirect effects through drug–drug interactions should be considered. Therefore, we recommend a critical evaluation of use and duration, as well as monitoring of psychotropic drug prescriptions at pre-assessment; we need to determine the possible interactions with drugs for coexisting physical morbidity, as well as drug–drug interactions with the proposed anesthetics—effects such as hemodynamic instability, including cardiac conduction changes, and the effects on CNS functioning in case of postoperative metabolic instability. A severity grading for drug–drug interactions pertinent to the anesthesiologist was presented in a recent overview.[13] It proposes the following classification: 1) *beneficial interactions*, where the combination is used to produce a useful and advantageous result for the patient; 2) *possible interactions*, where an interaction can be expected on a theoretical basis or because of pharmacological profiles of the drugs. Such interactions are known to cause minor-to-moderate changes in physiological functioning, and clinicians should be aware that an interaction of any severity is possible should these drugs be used again; 3) *interactions of note*, where the drug combination can have the potential to cause severe disturbances. Interactions of note are those where disturbances have been reported and where caution is necessary when the combinations are used; and 4) *hazardous interactions*, when the drug combination should be avoided. These concern well-documented interactions that have caused life-threatening incidents. The authors reviewed the available literature along these criteria but did not specify the criteria of their literature search. Other available ratings for the severity of drug–drug interactions, which broaden the scope beyond surgery, use comparable classifications.[16] Overviews of relevant interactions in comorbid patients seen in consultation–liaison practice have recently become available.[17,18] Given that drug–drug interactions result from individual profiles of drugs, and as drug development is an ongoing process, and new relevant complications of drugs or interactions are reported on a daily basis, the risk of individual drug–drug interactions should be assessed through available websites (Appendix 1).

Discontinuation: Preoperative Fasting and Route of Administration Another risk is related to the change of routes of administration of drugs because of the anesthesiological procedures. It influences the decisions concerning the (dis)continuation of drugs and the change to parenteral administration. Before surgery, the process of gastric-emptying is important for the timing of discontinuation of oral drugs. According to current knowledge, patients can use drugs with oral sips until 2 hours before the operation.[4,19,20] This is also in line with more recent recommendations of preoperative oral carbohydrate nutrition to prevent postoperative insulin-resistance in elective surgery.[21,22] Oral- and abdominal surgery might be an indication for an additional period of fasting. Oral surgery, such as in ear-nose-and-throat surgery, might be followed by the introduction of gastric tubes, which facilitates the application of nonparenteral drugs. Also, knowledge of intravenous and intramuscular replacement drugs is needed.[23]

Withdrawal and Psychiatric Recurrence or Relapse The risk of discontinuation of psychotropics for the induction of withdrawal syndromes, psychiatric recurrence, or relapse should be assessed. The first risk of discontinuation is the immediate effect of discontinuation in terms of physical and psychological withdrawal. The second risk of discontinuation is the risk of recurrence or relapse and its time relationship with withdrawal.

AVAILABLE EMPIRICAL EVIDENCE FOR THE SPECIFIC PSYCHOTROPIC GROUPS

A summary of the drug management characteristics for surgery patients is presented in Table 2.

Lithium

Pharmacodynamic and Pharmacokinetic Aspects Lithium gives relief of bipolar disorder by an unknown mechanism. Lithium is only available as tablets. After oral administration, lithium is well absorbed and distributed over total body water. Lithium is eliminated exclusively by renal excretion, with a half-life of 20–27 hours after a single dose. This might increase to 36 hours in case of chronic use. Lithium is glomerular-filtrated, and 80% is reabsorbed in the proximal tubulus. The reabsorption is related to sodium balance.

Direct Effects Lithium has a narrow therapeutic window. Toxicity is expressed by gastrointestinal symptoms, ECG changes, and CNS symptoms.[24] Lithium is well tolerated by the cardiovascular system. Its use is not absolutely contraindicated in patients with coexisting cardiovascular disease;[25] however, cases of changes of the smoothing of the T-wave,[26,27] ventricular arrhythmia,[28,29] and myocarditis[29,30] have been reported. Sinus dysfunction can lead to extreme atropine-resistant sinus bradycardia, which might happen with normal as well as toxic blood levels,[31–36] and might only become manifest during anesthesia.[37] Toxicity is related to plasma levels of more than 1.5 mmol/liter, but might occur at lower levels. When the plasma sodium concentration is low or when the patient is dehydrated, lithium clearance falls, and blood lithium levels rise. Lithium-related polydipsia, specifically when not compensated, and a complicated postoperative course are serious additional physical risks.[24]

Interactions The interaction with NSAIDs (nonsteroidal anti-inflammatory drugs) is reported as hazardous.[15,38] The toxicity of lithium can be increased by drugs that reduce lithium excretion or increase reabsorption in the kidney; these are drugs such as NSAIDs, ACE-inhibitors, thiazide diuretics, and metronidazole.[24,39] The effect of the loop diuretics on lithium excretion is far less than the effect of the thiazides. Furthermore, lithium clearance can be increased by CO_2-anhydrase inhibitors. The interactions with neuromuscular-blocking agents, specifically pancuronium and succinylcholine, are worthy of note.[15] The last affect both the latency and the reversal of neuromuscular blockade.[40]

Withdrawal and Psychiatric Recurrence or Relapse The available clinical evidence suggests that there is no withdrawal effect after abrupt discontinuation of lithium.[41,42] Abrupt discontinuation of lithium in a patient with bipolar disorder increases the risk of recurrence of the illness, especially mania, within the next few months. (No direct effects have been found.) This increased risk exceeds the risk of recurrence in the natural course of the illness.[43–45]

IV-IM Change and Alternative Drugs In regular clinical practice, there are no intramuscular (IM) or intravenous (IV) preparations of lithium available. Antipsychotics used in the acute phase of manic episodes are an option, specifically, haloperidol, as there is extensive experience with this drug in physically ill patients.[46] (See "First-Generation Antipsychotics" for listing of effects on cardiac conduction, such as QTc[47,48] [*www.qtdrugs.org*]).

Physical Status The greater the extent of the surgery and the higher the ASA classification, the higher the risk for complications due to dysequilibrium of electrolytes through gastrointestinal, cardiovascular, and renal dysregulations, and, therefore, the risk of further dysregulation, resulting in neurological complications.

Irreversible and Reversible Monoamine Oxidase Inhibitors (MAOIs)

Pharmacodynamic and Pharmacokinetic Aspects The irreversible MAOIs tranylcypromine and phenelzine and the selective and reversible MAOI moclobemide act by inhibition of the metabolic breakdown of norepinephrine and serotonin by the MAO enzyme. Thereby, they increase the level of norepinephrine and serotonin at the receptor site. Tranylcypromine and phenelzine irreversibly inhibit MAO, and, after cessation, it takes 1–4 weeks for the enzyme to regain its activity. Moclobemide is a reversible inhibitor, with an elimination half-life of 1–3 hours. All MAOIs are eliminated by hepatic metabolism.

Direct Effects There are no direct effects relevant for surgery.

Interactions Hazardous interactions in both reversible and irreversible MAOIs and anesthesia have been reported.[15] They include opioid analgesics (specifically peth-

TABLE 2. A Proposal for Psychotropic Drug Management in Patients in Need of Elective Surgery

Risks	Lithium	MAOIs	Tricyclics	SSRIs	First-Generation Antipsychotics	Clozapine
Direct effects	Hazardous: cardiac conduction; CNS; gastrointestinal	None	Hazardous: cardiac conduction; anticholinergic	Of Note: serotonergic, including gastrointestinal bleeding	Of Note: extrapyramidal symptoms; agranulocytosis; cardiac conduction changes; anticholinergic	Hazardous: agranulocytosis; seizures
Interactions	Hazardous: diuretics; ACE-inhibitors; NSAIDs	Hazardous: with epinephrine on RR; serotonergic	Hazardous: RR with sympathicomimetics; seizures with enflurane; P450 changes	Hazardous: P450 changes; serotonergics; Type I anti-arrhytmics; midazolam	Of Note: ACE-inhibitors; antacids	Hazardous: low RR Of Note: sedation
Need to discontinue	Yes	Yes	Yes	Not in ASA 1 and 2 patients	None	Yes
Withdrawal symptoms	None	Hazardous: nonselective, yes (hypertension); selective, none	Of Note: cholinergic rebound	Of Note: gastrointestinal; CNS symptoms	Of Note: Cholinergic rebound	Hazardous
Psychiatric relapse or recurrence	Hazardous	Unknown			Hazardous	Hazardous
Psychiatric consultation	Always	Always	Always	On indication	Always	Always
Integrated management	Always	Always	On indication	On indication	On indication	Always

Note: MAOIs: monoamine oxidase inhibitors; SSRIs: selective serotonin reuptake inhibitors; ACE: angiotensin-converting enzyme; RR: blood pressure; NSAIDs: nonsteroidal anti-inflammatory drugs.

idine), nefopam (a non-opioid analgesic), and sympathicomimetics. These interactions are twofold—effects on the blood pressure and on the CNS. Serious, including lethal, pressor effects have been reported because of interactions with indirectly-acting sympathicomimetic agents (amphetamine, ephedrine, metaraminol). These release intracellular stores of norepinephrine, and produce epinephrine-related hypertensive crises.[49,50] Directly-acting sympathicomimetic agents (norepinephrine, epinephrine, isoprenaline) are regarded as safer. However, in animal studies, a threefold potentiation of the pressor effect of epinephrine by moclobemide has been reported.[51] Epidural or intrathecal anesthesia results in a blockade of the sympathetic system. Consequently, on theoretical grounds, a combination of MAOI and such type of anesthesia is contraindicated. The few case reports in the literature are contradictory, however.[52,53] The reaction on the CNS has two mechanisms:[54] a Type I reaction is an excitatory form that is attributable to a central serotonergic overactivity; the serotonergic syndrome.[55,56] Pethidine, pentazocine, and dextromethorphan block presynaptic reuptake of serotonin. Therefore these drugs potentiate the development of a serotonin syndrome. In such patients, "MAOI-safe" surgery, which excludes pethidine (meperidine) and dextromethorphan and includes the use of morphine and fentanyl, is recommended.[57–59] The Type II reaction is a depressive form, and is supposed to be related to the inhibition of hepatic microsomal enzymes, leading to the accumulation of free narcotics and, as a result, CNS depression. Irreversible MAOIs need to be stopped for 2 weeks for the regeneration of MAO and normal monoamine metabolism. Even in such patients, cardiovascular collapse during anesthesia has been reported.[60] With morphine, a Type II (depressive) reaction has been reported.[54] Therefore, all reviews recommend discontinuation of the drug. As far as concerns about the discontinuation of the reversible MAOIs, the literature is contradictory.[51,61,62]

Withdrawal and Psychiatric Recurrence or Relapse Treatment with irreversible MAOIs is a clear indicator of psychiatric treatment of a disorder with a complicated course. Abrupt discontinuation of classical MAOIs can result in severe withdrawal syndromes presenting as medical emergencies such as serious depression, suicidality, hallucinations, and paranoid delusions. The withdrawal syndromes and, consequently, the prevention of an MAOI withdrawal-precipitated syndrome is a high priority.[63,64] It is not absolutely clear whether these are pure withdrawal symptoms or they reflect recurrence or relapse; there have been case reports of acute exacerbations.[64,65] From the surgical perspective, a period of discontinuation of 2 weeks of the irreversible blockade of MAO is needed for its restoration. It is suggested that patients on irreversible MAOIs could change some weeks before the surgery to reversible MAOIs, to reduce the period of discontinuation.[66] Because the effects of moclobemide discontinuation are reversed within 16 hours, and no (or only rare) withdrawal has been described, the period of discontinuation starts on the day of surgery.[62]

IV-IM Change and Alternative Drugs Generally speaking, there is no IV replacement available.

Physical Status The higher the chance of unstable blood pressure and its need for adjustment, the higher the chance of interactions between MAOIs and (indirect-acting) sympathicomimetics. The higher the chance of cardiovascular instability, the higher the chance of interactions.[15,67]

Tricyclic Antidepressant Agents

Pharmacodynamic and Pharmacokinetic Aspects Tricyclic antidepressants act by presynaptic inhibition of the uptake of norepinephrine and serotonin. They also block postsynaptic cholinergic, histaminergic, and alpha$_1$-adrenergic receptors. Tricyclic antidepressants are well absorbed in the gastrointestinal tract, but there is a large first-pass effect in the liver. Elimination is metabolic by Cytochrome P450 isoenzymes (Phase I metabolism), followed by conjugation of hydroxide metabolites (Phase II mechanism). In addition to the variation between the individual drugs of this class, there is also a large inter-individual variation; elimination half-life varies from 12 to 24 hours for extensive metabolizers to 3 days for poor metabolizers.[68]

Direct Effects All tricyclics lower the seizure threshold. The effects on the cardiac conduction system, such as QTc, and their relation to arrhythmias, have been amply described. The main effects are on rate, rhythm, and contractility through four mechanisms: 1) anticholinergic action; 2) interference with reuptake of adrenergic amines; 3) direct myocardial depression; and 4) alterations in membrane permeability.[48,69] The anticholinergic properties might induce an a-dynamic ileus, glaucoma, and postoperative delirium.

Interactions Hazardous interactions of tricyclics have been reported on blood pressure in combination with sympathicomimetics,[15] and induction of seizures has been re-

ported with enflurane.[15,70] Reported interactions of note are longer-lasting effects of antimuscarinics.[15] In patients using tricyclic and tetracyclic antidepressant agents, the circulatory effects of adrenaline and noradrenaline are potentiated, respectively, 2 and 9 times.[71] The mechanism of action of the resulting hypertensive crisis is related to the amine reuptake-blocking properties of the tricyclics.[72] Cardiac effects of atropine in patients treated with tri- and tetracyclic antidepressant medication were assessed in a prospective, controlled design. There was no evidence that these drugs rendered the heart more susceptible to the cardiac effects of atropine.[72] Recently, Malan et al.[73] reported severe, refractory hypotension during anesthesia in a patient on chronic clomipramine therapy. Hypotensive crises can be avoided by using indirect-acting sympathetic pressor amines.[67] The effects of norepinephrine might be reduced.[74]

Withdrawal and Psychiatric Recurrence or Relapse A large variation of withdrawal symptoms has been reported. The main group of symptoms is related to cholinergic withdrawal: gastrointestinal symptoms; symptoms of general malaise; and sleep disturbances, including vivid dreams and (hypo)mania. Also, there might be movement disorder-related symptoms, such as parkinsonism and akathisia and cardiac arrhythmia.[64] These symptoms appear during the first 2 days after discontinuation and last for about 2 weeks smoothed by gradual discontinuation.[64] In patients on maintenance therapy for depressive disorder who discontinue their medication, the relapse rate is estimated to be 2 to 4 times higher in the year after discontinuation, compared with those who continue.[75,76]

IV-IM Change and Alternative Drugs There is a large international variability in the availability of intravenous tricyclics. An exception might be clomipramine and amitriptyline.[23]

Physical Status A more extensive surgery implies a higher chance of instability of circulatory volume and related blood pressure. In patients using these tricyclics, the circulatory effects of adrenaline and noradrenaline are potentiated because of their amine reuptake-blocking properties.[15,67,71]

Selective Serotonergic Reuptake Inhibitors (SSRIs)

Pharmacodynamic and Pharmacokinetic Aspects The SSRIs at present comprise fluvoxamine, citalopram, sertraline, fluoxetine, and paroxetine. They act by presynaptic inhibition of serotonin reuptake. All drugs are orally well-absorbed and eliminated by hepatic metabolism. The elimination half-life of fluvoxamine is 17–23 hours and citalopram, 36 hours. Paroxetine has an elimination half-life of 24 hours, sertraline of 26 hours, and fluoxetine of 2–3 days. Sertraline and fluoxetine, however, are converted to active metabolites with an elimination half-life of 3–5 days and 7–9 days, respectively. The elimination half-life of fluoxetine and its active metabolite, norfluoxetine, are prolonged in cases of hepatic cirrhosis.

Direct Effects The direct effects of serotonergic reuptake inhibitors (SSRIs) are related to serotonergic potentiation and are therefore gastrointestinal symptoms, headache, anorexia, agitation, sleeplessness, and bleeding.[55,56,59,77] Except for the gastrointestinal effects (5% to 10%), the incidence of these phenomena is low. The increased risk of gastrointestional bleeding is about three times that of patients not using these drugs. The absolute risk is small and comparable to the risk in aspirin and NSAID use. This risk is increased when a combination of an SSRI and aspirin or an NSAID is used. In a recent cohort study in the Netherlands, the increased risk appeared to be related to the degree of serotonin-reuptake inhibition, being most elevated in fluoxetine, sertraline, clomipramine, and paroxetine use.[78] Also, SSRIs are among the psychotropics those with the highest risk of the development of the syndrome of inappropriate secretion of ADH (SIADH), sustained release of ADH resulting in hyponatremia, serum hypo-osmolality, and less than maximally-diluted urine. Although its mechanism is unknown, and SIADH is related to pulmonary and neurological diseases, as well as drugs, SIADH should primarily be seen as a direct effect of SSRIs.[79,80]

Interactions The interactions occur through the effects of the SSRIs on the Cytochrome P450 system (Phase I). Most important are inhibition of the metabolism through competition and the related increased serotonergic activity, which might result in a serotonergic syndrome. The most hazardous combinations are combinations of SSRIs or a combination of SSRIs with MAOIs or serotonergic TCAs such as clomipramine. Although no hazardous interactions in anesthesia are mentioned, the combination with pethidine, pentazocine, and tramadol can result in a serotonergic syndrome comparable with the combination of MAOIs.[15,56,58,59] In the anesthesia literature, avoidance of these opioid analgesics is recommended.[59] The literature

describes another mechanism for the development of a serotonin syndrome. The supposed mechanism is that competition with other highly protein-bound drugs—in this case, lidocaine, midazolam, and fentanyl—results in an increased free-drug fraction.[81] Because of the inhibition of one or more cytochrome P450 enzymes, a combination of enzyme-inhibiting psychotropic and type IC antiarrhythmic drugs with a narrow therapeutic window should only be given after consulting with a clinical pharmacologist experienced with drug–drug interactions. Because of inhibition of the cytochrome P450 3A4 by a metabolite of midazolam, combinations of SSRIs with midazolam should be monitored with caution, specifically when combined with fluoxetine. The same is true for the combination with warfarin, because of interactions with the CYP2C isoenzymes. An interaction relevant for the postoperative period is the inhibition of the metabolism of tramadol by paroxetine, resulting in excess sedation and an impairment of the analgesic action.[82] Because of genetic polymorphism, clinical implications vary in patients. Specific attention should be paid to possible interactions with drugs with a narrow therapeutic window.

Withdrawal and Psychiatric Recurrence or Relapse Withdrawal is a recognized clinical problem in SSRI use.[83–86] It is recognized in the anesthesiological literature as a reason for the continuation of these drugs during surgery.[66] The withdrawal symptoms are dizziness, lethargy, palpitations, gastrointestinal complaints, a flu-like syndrome, sensory phenomena, sleep disturbances, and psychic phenomena, such as anxiety, agitation, and tearfulness. There is a wide variety in the incidence of the withdrawal phenomena. The symptoms seem to be the most intensive in the SSRIs with a short half-life, specifically, paroxetine.

IV-IM Change and Alternative Drugs Parenteral forms of SSRIs are presently not readily available.

Physical Status As SSRIs tend to interact with other drugs through the P450 mechanism, it is not so much the extent of the surgery but the comorbidity that increases the risk of (avoidable) complications. Therefore, patients with a higher ASA classification potentially have an increased risk of (avoidable) complications.

Other Antidepressants

The risks of maprotiline can be compared with the tricyclics (see Tricyclic Antidepressant Agents: Interactions). It mainly inhibits norepinephrine reuptake. No explicit complications are mentioned in the literature in combination with surgery. Mianserine is an alpha$_2$ antagonist with alpha$_1$-, serotonin-, and histamine-antagonistic properties. Mianserine is regarded as cardiac-safe.[87] A special risk for mianserine is the higher incidence of neutropenia in elderly patients.[88] There is one case report in the Japanese literature of severe hypotension during anesthesia in a patient who used amantadine and mianserine.[89] Mirtazapine is an alpha$_2$-antagonist and also blocks serotonin and histamine receptors. No explicit complications are mentioned in the literature in relation to cardiac conduction or surgery. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor. At high doses, it also inhibits dopamine reuptake, but its clinical relevance is unclear. Because of its serotonergic characteristics, it might contribute, in combinations with other serotonergic drugs, to a serotonergic syndrome.[55,57] Venlafaxine has a low incidence of clinically significant increases in blood pressure.[90] No significant conduction abnormalities nor arrhythmias have been reported.[90] However, no studies with venlafaxine have been performed in cardiovascular-compromised patients.[90] Venlafaxine is, in-vitro, a weak inhibitor of CYP2D6, but it has less propensity for important metabolic interactions.[91] Except for fentanyl-induced rigidity during emergence from general anesthesia, until now, no serious complications during surgery have been reported.[92]

First-Generation Antipsychotics

Pharmacodynamic and Pharmacokinetic Aspects Antipsychotics block dopamine$_2$, histamine, α_1-adrenergic, and cholinergic receptors. The antipsychotic effect is probably based on their antidopaminergic action. Pharmacokinetics are highly variable, with half-life ranging from 2 hours, for droperidol, to 2 weeks, for the intramuscularly-administrated esterified depot preparations.

Direct Effects The main side effects of the first generation of antipsychotics are extrapyramidal symptoms. A seldom, but serious, complication of antipsychotic drugs is sudden death related to a prolongation of the QTc interval and torsades des pointes. The problem is most evident in the phenothiazines, specifically thioridazine. These drugs are nowadays replaced by high-potency antipsychotics, in which sudden death is less a problem. Therefore, there is a need for careful preoperative evaluation and perioperative cardiac monitoring for electrocardiographic changes in patients using antipsychotic agents.[47,48,93]

Interactions No hazardous interactions are mentioned for phenothiazines.[15] Hypotension is reported as a hazardous interaction in combinations of haloperidol or droperidol with ketanserin, a serotonergic $5HT_2$ antagonist with weak selective $alpha_1$-receptor blocking properties. Seizures are reported with desflurane, a volatile anesthesia.[15,94] Interactions of note are reported for the phenothiazines with antimuscarines. Clinically-relevant interactions with other classes of first-generation antipsychotics are not mentioned in most reviews. Potentiation of the effects of narcotic analgesics is reported. Chlorpromazine and thioridazine, which can selectively block α-adrenergic receptors, might lead to interactions with drugs with sympathicomimetic action, such as epinephrine, resulting in vasodilatation and hypotension.[67] With halogenated inhalation anesthetics, hypotension has been reported for several antipsychotic agents. Excess central and peripheral anticholinergic effects have been reported in elderly patients in combinations of chlorpromazine or thioridazine with atropine or scopolamine.[67]

Withdrawal and Psychiatric Recurrence or Relapse There are withdrawal symptoms comparable to the cholinergic rebound effect described for the tricyclic antidepressant agents. These symptoms appear 1 to 4 days after discontinuation and abate over 7 to 14 days.[64,95] There is an argument that early relapse is related to dopaminergic hypersensitivity of the brain due to pharmacological withdrawal, whereas the delayed relapse might reflect the natural course of the illness.[96] In a metaanalysis including 66 articles and 4,365 patients with schizophrenia, it is reported that patients who continue antipsychotics, in contrast to those who stop, the relapse rate is 16%, versus 53% for those who stopped over a mean period of 9.7 months. The relapse rate is much higher in patients who stop suddenly. In those who stop abruptly, within 10 weeks, 25% had symptoms, and, after 30 weeks, 50% had symptoms.[95]

IV-IM Change and Alternative Agents Haloperidol is the best known intravenous preparation, especially in medically ill persons, as it is the drug of choice in delirium patients.[48,97] Still, haloperidol carries the risk of torsades de pointes, arrhythmias, and neuroleptic malignant syndrome.[47,49,93]

Physical Status The extent of surgery does not seem to influence the interactions between anesthesia and antipsychotics. Combinations of certain antipsychotics and anesthetics should be avoided. The main risks seem to be related to other existing physical comorbidity, such as cardiac pathology, influencing the conduction system, or infectious or cerebral pathology, which is a risk of the induction of a neuroleptic malignant syndrome.

Second-Generation Antipsychotics

The empirical evidence of possible interactions with anesthetics is almost lacking. However, it is evident that the use of these drugs, which have an advantage in the treatment of patients with schizophrenia because of their lack of extrapyramidal effects, can result in medical complications, such as weight gain, diabetes, and an increase in lipids, as well as sudden death due to torsades de pointes.[48,98]

Clozapine

The main clinical complications reported are agranulocytosis and hyperthermia. It affects cardiac conduction.[99] During anesthesia, hypotension has been reported.[100] In case of discontinuation of clozapine, dystonias, dyskinesias, delirium, and rapid onset of psychosis have been reported, which require emergency psychiatric-specialist intervention.[101,102]

DISCUSSION

The available empirical evidence is—except for the risk of withdrawal and relapse of psychiatric illness—on the level of nonsystematic reviews and case reports. Despite the fact that a systematic review of this multidimensional topic would be preferred, we decided that it would be too complicated and would be based on a low level of evidence. We came to the conclusion that it would not result in a level of empirical evidence superior to expert opinion. Consequently, the proposal is based on available literature, expert opinions, and integrated thinking. Therefore, the proposal serves to support clinical reasoning. Specifically, in cases with complex psychiatric illness, patient-oriented perioperative management needs to be prepared by the involved physical specialist, the anesthetist, the psychiatric consultant, and the outpatient psychiatrist. The literature suggests that the risk of psychotropics in surgery is primarily related to the type of psychiatric disorder, the psychotropic drug, physical comorbidity, and related drugs. The extent of surgery seems less relevant. Therefore, in every patient who uses psychotropics and is in need of surgery, psychotropic drug management should be considered. The perioperative risk related to psychotropics in-

creases in combination with physical illness. In terms of ASA classification, patients who use psychotropics qualify at least for an ASA Classification 2: Physical complications from mild systemic disease contribute to postoperative morbidity and mortality.[9] We suggest following Dawson's classification for quantification of the seriousness of drug–drug interactions as well as for the direct effects of the drugs; these are then linked to the ASA classification system.[15] Possible interactions are suggested to be rated as ASA 2, whereas interactions of note and hazardous interactions should be rated as ASA 3. The issue of preoperative fasting relevant to patients who can continue drugs, seems to offer more flexibility nowadays. Intravenous administration of psychotropics only seems indicated in patients with unstable psychiatric disease, such as psychosis or bipolar disorder.

PROPOSAL

General Aspects

The physical perioperative risk of patients who use psychotropics is such that, from a preventive perspective, they require systematic evaluation integrated into preoperative assessment. Patients who use lithium, MAOIs, tricyclics, and clozapine have hazardous drug interactions, with serious physical risks, including withdrawal, which cannot be avoided. Therefore, such patients qualify for ASA Classification 3. From the perspective on the management of the physical risk, they require drug discontinuation. Because the risk of acute withdrawal is high and there is a risk of psychiatric relapse or recurrence, these patients require intensive individualized integrated anesthetic/intensivistic/psychiatric management. In patients on SSRIs who are mentally and physical stable (ASA Classification 1), the risk of withdrawal seems to justify their continuation. Patients who use other psychotropics should be regarded as qualifying for ASA Classification 2 and require individualized evaluation of their perioperative risks.

Lithium

Lithium's direct effects cause hazardous risks in surgery. This is specifically true when hemodynamic instabilities occur, and renal excretion becomes impeded through interference with sodium and potassium metabolism. The physical risk of intoxication, with its detrimental and fatal risks for the CNS, is unacceptable. Therefore, lithium discontinuation is recommended. Lithium can be stopped at once because no withdrawal symptoms occur. Patients' fluid intake should be thoroughly assessed to adjust perioperative intravenous hydration in case of polydipsia as clinical manifestation of a partial diabetes insipidus. Also, thyroid hormones, sodium, potassium, and creatinine should be assessed. Taking a half-life of 24 to 36 hours into account, we propose that lithium be discontinued 72 hours before surgery. When postoperative, and the patient has normal ranges of potassium, sodium, and creatinine, is hemodynamically stable, and is able and allowed to drink, lithium should be restarted, with control of blood levels, within 1 week. This is most important because the psychiatric risk of recurrence or relapse is hazardous. The same drug regimen should be provided as in the preoperative period unless kidney function has declined (in case of a caesarean section, the dosage needs adjustment because of shifts in fluid distribution).[103] Patients should always be seen by a consulting psychiatrist. An integrated anesthetic/intensivistic/psychiatric management should be decided upon.

The only reason not to stop lithium treatment is minor surgery, with local anesthesia, meaning infiltration anesthesia, for an atherome cyst, but not using larger nerve- or central blockades.

MAOIs

There are two hazardous risks of drug–drug interactions. The serotonergic risk (Phase I) can be prevented by avoiding drugs that prevent presynaptic uptake of serotonin, such as pethidine, pentazocine, and dextromethorphan. The risk of hemodynamic instability is less controllable. Therefore, we recommend that irreversible MAOIs be discontinued. When discontinued, they can be restarted when the patient is hemodynamically stable, is able and allowed to drink, and is not on new, potentially interacting drugs. One strategy to discontinue irreversible MAOIs is to change, in the weeks before surgery, to a reversible MAOI. The reversible MAOI moclobemide only needs to be discontinued for 24 hours to restore the depleted neurotransmitters. It can be restarted as soon as the patient is hemodynamic stable and is able and allowed to drink. However, patients have a serious risk of withdrawal, psychiatric relapse, or recurrence. These patients should always be seen by (their) psychiatrists. An integrated anesthetic/intensivistic/psychiatric strategy should be decided upon.

The only reason not to stop MAOIs is minor surgery, with local anesthesia, meaning infiltration anesthesia for an atherome cyst, but no larger nerve- and central blockades.

TCAs

There are two hazardous drug interaction risks to be avoided: the direct effects on the cardiac system and the interactions with anesthetic drugs regulating the cardiovascular system. However the literature is controversial. Therefore, we suggest discontinuation of TCAs in all patients with ASA Classification of 2 and higher, even in minor surgery with local anesthesia. Because abrupt discontinuation can cause serious withdrawal symptoms, the drugs should be gradually discontinued over 2 weeks before surgery. We recommend a preoperative ECG after discontinuation to have a baseline assessment before surgery. When, postoperatively, the patient is hemodynamically stable, is able and allowed to drink, and is not on new, potentially interfering drugs, the medication should be restarted. Specifically, in elderly patients, this start should be gradual because of possible orthostatic effects. When the patient is mentally stable, there is no need for a psychiatric consultation. Specifically, patients with more complex physical comorbidity and unstable psychiatric illness should be seen by their psychiatrist.

SSRIs

The risks of drug interactions with SSRIs are important. They are related to serotonergic effects of pethidine, pentazocine, and dextromethorphan, which prevent presynaptic uptake of serotonin and might induce a serotonergic syndrome. The interactions can be avoided by serotonin-free anesthesia and analgesia. Interactions with existing physical illness and the related drug regimens should have been taken into account at initiation of therapy. Discontinuation can cause withdrawal symptoms, specifically in the short-acting SSRIs. Therefore, we propose that SSRI not be discontinued in order to prevent anesthetic interactions. The exception to this rule should be when the SSRI is used in combination with aspirin or an NSAID and when the SSRI is used in patients over 80 years of age. In these patients, the balance of risks of withdrawal and bleeding should at least be discussed. As long as the patient is preoperatively assessed and recorded as mentally stable, there is no need for a psychiatric consultation.

Other Antidepressants

Compared with the other drugs—except for the pressure-effects of maprotiline—the available evidence of the risks of perioperative complications of maprotiline, mianserine, mirtazapine, and venlafaxine is thin. No serious complications are described in the literature. There is a risk of withdrawal symptoms, however. When the patient is mentally stable, there is no need for a psychiatric consultation. Specifically, in patients with more complex physical comorbidity (ASA Classification 2) and with unstable psychiatric illness, they should be both seen by their psychiatrist and anesthesiologist. They should balance the risks and decide on individualized management.

First-Generation Antipsychotics

The potentiation of sedation is an interaction of note and a controllable phenomenon. The anesthesia literature is quite conclusive about the continuation of the drug in the perioperative period. As ECG abnormalities occur in these patients, a preoperative ECG should be done and evaluated for a prolonged QTc interval in patients with comorbid physical illness (ASA 2).[43] Patients should be seen by their psychiatrist in the perioperative period.

Second-Generation Antipsychotics

There is not enough evidence for a specific proposal. It is proposed that patients should be seen by their psychiatrist and an integrated anesthetic/psychiatric regimen should be decided upon.

Clozapine

Clozapine has hazardous risks of drug interactions resulting in effects on circulation. This risk requires drug discontinuation. Discontinuation of clozapine can cause hazardous withdrawal phenomena. Moreover, patients treated with clozapine have a high risk of psychiatric recurrence or relapse. Therefore, we recommend psychiatric consultation well in advance of surgery to come to an integrated anesthetic/intensivistic/psychiatric management plan.

CONCLUSION

The intention of the proposal is to stimulate the development of a preventive, integrated risk assessment in psychiatrically vulnerable patients using psychotropic drugs and who are in need of elective surgery. The presented model allows indicator-based integration in pre-assessment clinics through use of the ASA classification system. Indications for perioperative psychotropic risk management,

including psychiatric referral, have been operationalized. This could be combined with a more generic assessment of integrated health risk and needs, such as is possible with the INTERMED method.[104,105] Such a model would allow for the prediction of outcomes of surgery, practice audit, and research. Regarding the size of the problem, the vulnerability of the patients and the often-lacking reimbursement as part of health plans, this is an area that deserves a more proactive approach in order to enhance the quality of surgical care.[106]

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APPENDIX 1. Websites for Information on Drug–Drug Interactions

http://www.drugdigest.org/dd/Interaction/ChooseDrugs/1,4109,00.html
http://medicine.iupui.edu/flockhart/
http://www.dal.ca/~pharmwww/druginfo/drugprobleminteraction.html

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