Perioperative Management of Antidepressants and Herbal Medications in Elective Plastic Surgery

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Background: Patients seeking elective aesthetic surgery often use herbal medications and/or antidepressants. As the popularity of these medications grows, the plastic surgeon must become familiar with these drugs and their potentially harmful effects during the perioperative period.
Methods: The authors performed a PubMed search to identify commonly used herbs and antidepressants and their effects on patients during elective cosmetic surgery.
Results: Case series, studies, and reviews for 29 of the most common herbs and antidepressant medications were obtained from this search. On the basis of the existing data, the authors established recommendations for the management of these medications before elective cosmetic surgery.
Conclusions: Most commonly used herbs and antidepressant medications have potentially deleterious effects on the patient during surgery, ranging from increased risk of bleeding to fatal interactions. The plastic surgeon must be familiar with these drugs to manage these patients appropriately. (*Plast. Reconstr. Surg.* 123: 377, 2009.)

Antidepressants and herbal medications have become mainstays within the pharmacopeia of the elective plastic surgery patient. Freedman[1] and colleagues reported that 17 percent of their cosmetic patients were on at least one antidepressant. The National Center for Health Statistics estimated that $118 million (or nearly 5 percent) of the $2.4 billion spent on prescription medications in the United States in 2005 was on antidepressants.[2] In 2000, Kaye et al. identified 32 percent of the ambulatory surgery population as using herbal medications.[3]

Complications of these medications when mixed with anesthesia and the stress of surgery range from increased risk of bleeding to central nervous system and cardiac effects to death. Each surgical team must evaluate the preoperative patient's medications and weigh the risks associated with them. Unfortunately, there are minimal published data in the form of randomized clinical trials, meta-analyses, or firm practical guidelines. Instead, the surgeon must rely on anecdotal experience, advice from the anesthesiologist and primary care physician, and case reviews in the literature to make an informed decision. This study sought to identify common antidepressants and herbs and then provide guidelines for their management in the preoperative period.

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MATERIALS AND METHODS

A PubMed database search was conducted using the terms "antidepressants and surgery," "herbs and surgery," "antidepressants and anesthesia," and "herbs and anesthesia." The search was conducted for articles between January of 1966 and January of 2008. No randomized clinical trials were identified, but reviews and case studies were identified that discussed the effects of antidepressants and herbs on anesthesia and surgery.

RESULTS

Table 1 summarizes the physiologic effects of antidepressants during the perioperative period.

Tricyclic Antidepressants

Tricyclic antidepressants act by presynaptic inhibition of the uptake of norepinephrine and/or

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Table 1. Antidepressants and Effects on Perioperative Patients

Medication	Central Nervous System Effect	Cardiovascular Effect	Increased Risk of Bleeding	Other
Tricyclics		+		
Lithium	+	+		Renal toxicity
MAOI	+	+	+	
SSRI	+		+	
Venlafaxine		+		
Bupropion	+	+	+	
First-generation antipsychotics	+	+		Torsades de pointes
Second-generation antipsychotics	+			Torsades de pointes
Clozapine		+		
Propanolol		+		Avoid epinephrine
Sumatriptan, avitriptan		+	+	

MAOI, monoamine oxidase inhibitor; SSRI, selective serotonergic reuptake inhibitor.

serotonin. Tricyclic antidepressants have been linked to anticholinergic effects, coma, dysrhythmias, hypotension, and death. Seizures have been documented when tricyclic antidepressants have been combined with enflurane.[4] Most concerning are the cardiac effects, which appear to be mediated by both a direct decrease in myocardiac contractility, resulting in hypotension, and slowing of sodium channel electrical conduction, resulting in dysrhythmias.[5]

One study isolated human atrial cardiac tissue and set up an in vitro study that measured heart contractility when the cardiac tissue was bathed in increasing solutions of desipramine or amitriptyline.[6] They found a direct correlation between decreased force of contractility of the heart and increasing levels of tricyclic antidepressant drugs. This is hypothesized to be the mechanism for tricyclic antidepressant–mediated hypotension.

Lithium

Studies have documented the toxicity derived from increased lithium levels when lithium is mixed with nonsteroidal antiinflammatory drugs.[7] Lithium also interacts with neuromuscular-blocking agents including pancuronium and succinylcholine and increases the duration of these drugs, thereby making reversibility of these drugs more difficult.[8] Other possible effects of lithium in combination with other agents include myocarditis, ventricular dysrhythmia, polydipsia, and renal failure.[9] Abrupt discontinuation of the drug has not demonstrated any withdrawal effects, so this should be a strong consideration for surgery.

Monoamine Oxidase Inhibitors

Both irreversible (tranylcypromine and phenelzine) and reversible monoamine oxidase inhibitors (moclobemide) act by inhibition of the monoamine oxidase enzyme in the breakdown of norepinephrine and serotonin, thereby increasing the circulating concentration of the latter two neurotransmitter agents. Dangerous interactions such as hypertensive crises can occur when monoamine oxidase inhibitors are mixed with sympathicomimetics such as epinephrine.[10] Another well-known interaction is between monoamine oxidase inhibitors and meperidine, which may lead to hypertension, agitation, rigidity, convulsions, and hyperthermia.[11]

In addition, the block in reuptake of serotonin by drugs such as meperidine and dextromethorphan can result in serotonin syndrome when combined with monoamine oxidase inhibitors.[12] These symptoms manifest as agitation, tremors, hyperthermia, myoclonus, and hypertension.

Monoamine oxidase inhibitor interactions can also exhibit a depressive form that stems from the inhibition of hepatic microsomal enzymes, leading to the accumulation of free narcotics and cardiac and/or central nervous system depression. This reaction has been reported when morphine was combined with a monoamine oxidase inhibitor.[13]

Selective Serotonergic Reuptake Inhibitors

These increasingly popular drugs include fluvoxamine, citalopram, sertraline, fluoxetine, and paroxetine. They act to increase serotonin levels by presynaptic inhibition of serotonin uptake.

Direct effects of these drugs from serotonin potentiation include bleeding, gastrointestinal symptoms, headache, agitation, and insomnia.[14] Particularly when combined with aspirin or a nonsteroidal antiinflammatory drug, use of selective serotonergic reuptake inhibitors requires added vigilance on the part of the surgeon during hemostasis.

The combination of these drugs with meperidine, pentazocine, and tramadol has resulted in documented serotonergic syndromes comparable with the monoamine oxidase inhibitors.[9,15] The interaction of tramadol given postoperatively with selective serotonergic reuptake inhibitors can result in excess sedation and impairment of analgesic actions. When administering midazolam or lidocaine with selective serotonergic reuptake inhibitors, one should proceed with extreme caution because of the prolonged effects of selective serotonergic reuptake inhibitors that can result, especially when combined with fluoxetine.[15] Withdrawal symptoms such as lethargy, palpitations, and gastrointestinal tract disturbances are documented issues with cessation of these drugs, so careful discussion with the psychiatrist, surgeon, and anesthesiologist may be warranted.[16,17]

Venlafaxine (Effexor; Wyeth Pharmaceuticals, Inc., Madison, N.J.) is a nonselective selective serotonergic reuptake inhibitor and inhibits norepinephrine, serotonin, and dopamine reuptake. It was the sixth most popularly prescribed antidepressant in 2006 and has been used in diabetic neuropathy and migraines in addition to depression.[9] Halogenated anesthetic drugs have been shown to decrease the reuptake of serotonin and inhibit the metabolism of serotonin, particularly within the pulmonary system.[18–20] When combined with halogenated anesthetic drugs, venlafaxine and other selective serotonergic reuptake inhibitors can lead to serotonin syndrome and documented increases in blood pressure.[21]

Another very popular atypical antidepressant, bupropion (Wellbutrin; GlaxoSmithKline, Middlesex, United Kingdom), was the fourth most widely prescribed antidepressant in 2006; its sales continue to increase because it is also used as a smoking-cessation agent.[22] It is unique in that it has both norepinephrine and dopamine neurotransmitter activity, without known changes in serotonin levels.[23] It was hailed for not possessing the sexual dysfunction side effects of the selective serotonergic reuptake inhibitors but does have other notable adverse effects, including increased susceptibility to seizures, central nervous system disturbances such as psychosis and hallucinations, and cardiac effects such as tachycardia and hypertension.

Extensive study of bupropion and anesthesia and/or surgery does not exist, but one study examined the effect of bupropion on anesthetized dogs.[24] The investigators found a dose-dependent increase in pulmonary arterial pressure and vasculature.

First-Generation Antipsychotics

These agents (e.g., haloperidol) block dopamine, histamine, cholinergic receptors, and α_1-adrenergic receptors. There is a well-documented chance of sudden death with these drugs caused by prolongation of the QTc interval and torsades des pointes.[25] Seizures have been reported when these agents are given with desflurane, and potentiation of narcotics must be considered as well. There have also been reports of hypotension with halogenated inhalation anesthetics.[26]

Second-Generation Antipsychotics

The newer line of antipsychotics has replaced the first-generation antipsychotics because of their lack of extrapyramidal effects. However, they also can result in sudden death caused by torsade de pointes; thus, medications that prolong the QT interval such as droperidol should be avoided.[27]

Clozapine

Clozapine is an atypical antipsychotic that has gained notoriety for its side effects that include leukopenia and myocarditis. Reports of hypotension during anesthesia and changes in cardiac conduction may occur.[28,29] This is another drug that features rapid withdrawal symptoms and merits discussion with a psychiatrist.

Propanolol

Although not a classic antidepressant, this medication may be taken as an anxiolytic for stage fright and anxiety situations. In 1982, Foster and Aston reported six case studies that highlighted the dangerous interactions between propanolol and epinephrine.[30] The latter is a nonselective β-blocker commonly used to preinject surgical sites; the former is a commonly prescribed α- and β-agonist used in cardiac dysrhythmias, hypertrophic subaortic stenosis, pheochromocytoma, angina, hypertension, migraine headache, stage fright, and tremors.

The combination of the two drugs can lead to a hypertensive episode followed by a profound reflex bradycardia. It is thought that the β-agonist activity of epinephrine is blocked peripherally by propanolol, thus accentuating the α_1-agonist activity of epinephrine.[31,32] This results in significant hypertension, which is the first manifestation of this response. A reflex bradycardia mediated by vagally innervated baroceptors then ensues, and the β-blocked myocardium is unable to increase cardiac output in the face of increased peripheral

resistance. Ultimately, this can lead to both hypertensive strokes and/or cardiac arrest.

Intraoperative treatment is predicated on recognition of this event and may require the use of atropine and vasodilatory therapy. More selective β_1-blockers such as metoprolol do not seem to cause these pathognomonic hypertensive bradycardic episodes.[33]

Sumatriptan and Avitriptan

These medications are prescribed in the treatment of migraine headaches, which often plague the patient diagnosed with depression. This can cause serotonin syndrome when combined with selective serotonergic reuptake inhibitors.[34] One hundred fifty milligrams of avitriptan demonstrated reproducible, dangerous increases in blood pressure in one randomized controlled study.[35] Case reports have demonstrated increases in systemic and pulmonary blood pressure and coronary artery vasoconstriction after sumatriptan administration as well.[36,37] Even more dangerous are the cardiac interactions that can take place when sumatriptan is administered in combination with the stress of surgery.[38]

Herbs

Table 2 provides a brief summary of the effects of herbs during the perioperative period.

Herbs are seed-bearing plants that exhibit medicinal and/or aromatic properties. They have been used extensively in the Far East and have enjoyed a surge of popularity in the United States, with billions of dollars in sales each year.[39,40] Heller and colleagues reported that 55 percent of cosmetic surgery patients in their study were taking at least one of 11 common herbs.[41] Numerous studies have demonstrated adverse effects, and the surgical team must be cognizant of the dangers that herbs present when combined with anesthetic drugs and the stress of surgery.

Garlic

This common herb reduces atherosclerosis and blood pressure through its anticholesterolemic and vasodilatory effects. However, its active ingredient, allicin, also works to prevent platelet aggregation and may potentiate bleeding.[42] At least one patient developed a spontaneous epidural bleed that was attributed to garlic use.[43]

Gingko

This popular herb is used for a myriad of indications, including vertigo, claudication, tinnitus, sexual dysfunction, and dementia and other cognitive disorders. Gingko seems to work as a platelet-activator factor inhibitor and a modulator of nitrous oxide, both of which may also increase bleeding.[44] Case studies include spontaneous hyphema and four cases of spontaneous intracranial bleeding caused by its use.[45–47]

Ginseng

Popular in Asia, this herb has been used to treat stress and imbue virility. Ginsenosides have been shown to inhibit platelet aggregation in vitro and prolong both coagulation time and activated partial thromboplastin time.[48] Hypertension, emesis, epistaxis, and Stevens-Johnson syndrome have also been documented with this herb.[49,50] Finally, ginseng has the potential to cause hypoglycemia and should be avoided in diabetics, potentially leading to labile glucose levels intraoperatively, especially because preoperative patients have

Table 2. Effects of Herbs and Supplements on the Perioperative Patient

Herb or Supplement	Central Nervous System Effects	Cardiovascular Effects	Increased Bleeding	Other
Garlic			+	
Gingko			+	
Ginseng			+	
Ginger			+	
Feverfew			+	
Kava	+	+		
St. John's wort	+	+	+	
Valerian	+			
Ephedra		+	+	
Echinacea		+		Hepatoxicity
Dong quai			+	
Licorice		+	+	
Mafesian		+		
Goldenseal		+		Electrolyte disturbances
Milk thistle				Electrolyte disturbances
Marijuana	+			Bronchospasm
Fish oil			+	
Glucosamine			+	

been fasting.[41] Ginseng has been ascribed responsibility for one death when it was combined with ma huang.[51]

Ginger

This fragrant herb has been prescribed for vertigo, motion sickness, nausea, and hyperemesis gravidarum. It is a known potent inhibitor of thromboxane synthetase enzyme and therefore can increase bleeding times.[52]

Feverfew

Used to treat migraine headaches, feverfew acts to inhibit serotonin release and inhibit prostaglandin production. Because of its antiplatelet activity, bleeding complications may increase.[53]

Kava

This diverse herb, made from the plant *Piper methysticum*, has been used as an anxiolytic, for gonorrhea treatment, and for certain skin disorders. Kava has dose-dependent effects on the central nervous system and can potentiate benzodiazepines and cause lethargy and disorientation by binding to the γ-aminobutyric acid receptor α-subunit and causing neuronal cells to become resistant to excitation.[54] Furthermore, dose-dependent vasodilation through noncompetitive inhibition of sodium channel receptors and direct myocardial depression results in hypotension.[55]

St. John's Wort

This ubiquitous herb is also known as hypericum perforatum and is used to treat mild to major depression, anxiety, and sleep disorders. It seems to act by inhibiting serotonin, norepinephrine, and dopamine reuptake by neurons. This is especially a concern if taken in combination with selective serotonergic reuptake inhibitors and may potentiate midazolam and lidocaine. The active ingredient, hypericin, also acts as an irreversible inhibitor of monoamine oxidase A and B.[56] This may lead to the documented deleterious effects of anesthetics in combination with monoamine oxidase inhibitors.

Valerian

This herb acts as a sedative and is used as a sleep aid. Valerian acts through γ-aminobutyric acid modulation, which can potentiate the effects of sedatives administered during anesthesia.[44]

Ephedra

Also known as ma huang in China, ephedra is used to treat flu, colds, bronchitis, low blood pressure, and respiratory ailments such as asthma. This drug has become increasingly popular among cosmetic surgery patients; one study identified 18 percent of cosmetic patients as taking this herb.[41] It contains ephedrine, pseudoephedrine, and methylephedrine, and causes an increase in blood pressure and heart rate. Ma huang stimulates α_1, β_1, and$_1$ activity, which can lead to stroke and myocardial infarction, particularly if given with halothane or monoamine oxidase inhibitors.[57] Documentation of multiple fatalities with this drug is present in the literature.[58]

Echinacea

These herbs are members of the daisy family and may be used to increase energy and activity in patients suffering from arthritis. Chronic use of this medication may cause tachyphylaxis. Of greater concern is a documented case of anaphylaxis when combined with general anesthesia.[59] Finally, hepatotoxicity is a possibility also if combined with other anesthetic hepatotoxic agents, because echinacea is an inhibitor of the cytochrome P450 3A4.[60]

Dong Quai

Dong quai is prescribed for menopausal or menstrual complaints. It contain six Coumadin derivatives, which are thus vitamin K antagonists. The risk of bleeding must be recognized in patients taking this medication preoperatively.[61]

Licorice Root

Popular for heart and gastrointestinal "problems," licorice root may lead to hypertension, sodium retention, hypokalemia, and generalized edema. This herb is thought to disrupt the metabolism of corticosteroids and results in increasing the half-life of cortisol and aldosterone.[62] The stress of surgery may augment these responses and lead to homeostatic disturbances in the perioperative period.

Mafesian

An analgesic for joint pains and arthritis, mafesian binds to sodium channels and leads to continued excitation. This in turn leads to ventricular dysrhythmias and compromised respiration, which may be exacerbated by the stress of surgery and anesthesia.[63]

Goldenseal

This herb is a laxative used in patients suffering from constipation and bowel immotility. As such, it may cause electrolyte imbalances in the patient and should be discontinued before surgery along with other laxatives.[63] Laboratory results should be obtained 2 to 3 weeks after these drugs are stopped to verify normalization of electrolytes.

Milk Thistle

This medication is thought to be hepatoprotective, immunomodulating, and antioxidant inducing. Cirrhotics and patients suffering from gallbladder disease or hepatitis have embraced this alternative medication for relief. The active

agent is silymarin and it is thought to reduce insulin resistance and lower cholesterol. However, similar to goldenseal, a laxative effect has been reported, which can disrupt electrolyte levels preoperatively.[64] There are also reported headaches, which can exacerbate nausea and emesis.

Marijuana

This controlled herb is derived from the plant *Cannabis sativa*, and its most potent psychoactive agent is delta^9-tetrahydrocannabinol. There are approximately 340 other chemical compounds in cannabis, and smoke from a marijuana cigarette contains carbon monoxide and tars as found in cigarettes.[65] In 1999, Ashton noted that anywhere from 10 to 30 percent of 20- to 30-year-olds undergoing surgery at his institution may have used marijuana, and its use continues to spread in the United States.[65]

Cannabis is well known to cause euphoria, dysphoria including panic attacks, and a depressant central nervous system effect after the initial euphoric phase. Chronic use of cannabis is associated with bronchitis, emphysema, and squamous cell metaplasia of respiratory tisues.[66] Video bronchoscopy performed by Roth and colleagues led the authors to conclude that airway inflammation in marijuana smokers is similar in frequency, type, and magnitude to that in tobacco smokers.[67] Chronic use of cannabis can cause acute respiratory obstruction through edema.[68]

Cavero and colleagues found that delta^9-tetrahydrocannabinol produced bradycardia in dogs in a dose-dependent manner in anesthetized dogs.[69] The authors observed no change in peripheral vasodilation, but a reproducible bradycardic effect was noted. Conversely, a case report involving a marijuana user reporting tachycardia was noted after delta^9-tetrahydrocannabinol injection was given as a premedicant sedative.[70] Elimination of delta^9-tetrahydrocannabinol from neural tissue takes approximately 30 days, and the half-life in the liver is approximately 50 hours.[71]

Common Supplements

Two common supplements are also mentioned because of their widespread use and potential for increased risk of bleeding during the perioperative period.

Fish Oil

Prized for its high concentrations of omega-3 fatty acids, fish oil has been consumed for its presumed ability to decrease cardiac heart disease. It has been shown to decrease triglyceride levels and reduce blood pressure in hypertensive patients, and has been hypothesized to even decrease the risk of sudden death syndrome.[72] Bleeding times measured in Greenland Eskimos who imbibed fish oil demonstrate increased bleeding times.[73] Fish oils have been shown to increase levels of plasminogen tissue activator and decrease concentrations of plasminogen inhibitor as well.[74]

Glucosamine

Often combined with chondroitin sulfate, glucosamine has become nearly ubiquitous in the United States in patients suffering from arthralgia and osteoarthritis. Glucosamine is an amino monosaccharide and chondroitin is a glycosaminoglycan found in cartilage. The popularity of these supplements has resulted in a large, multicenter study, the Glucosamine/Chondroitin Arthritis Intervention Trial, being launched in the United States to examine their effects.[75]

The concern with regard to surgery is that glucosamine inhibits platelet activation. Guinea pigs receiving 400 mg of glucosamine were found to have suppressed platelet activation by 51 percent in one study, and it is believed that this activity is modulated by suppression of adenosine triphosphate release and thromboxane A2 production.[76]

DISCUSSION

That the industry of antidepressant and herbal medications is growing is clear in both pharmaceutical sales analyses and the anecdotal experience of almost every plastic surgeon. In today's medicolegal environment, the plastic surgeon must be familiar with these medications in the patient seeking elective plastic surgery.

Unfortunately, comprehensive, randomized trials that focus on these medications and their safety in surgery do not exist. Instead, the highest level of evidence exists in case studies and reviews that document the deleterious potential of mixing these drugs with anesthesia and surgery. Furthermore, the exact incidence of these complications is unknown because it has not been studied for these drugs. Therefore, recommendations based on our study are based on limited publications, our anecdotal events, and the relatively benign effects of discontinuing these drugs before surgery with the guidance of a psychiatrist and/or an internist.

The following recommendations are based on our opinions after review of the existing literature and our own anecdotal experience. Because of the large number of case studies documenting adverse effects of tricyclic antidepressants and anesthesia, we recommend discontinuation of these medications 2 weeks before surgery if approved by a psy-

chiatrist. If tricyclic antidepressants are continued during surgery, the surgical team must be vigilant for autonomic instability in the perioperative period. Lithium does not possess strong withdrawal effects, and its potential for autonomic instability should lead to cessation of its use 2 weeks before surgery.

In general, we recommend discontinuation of irreversible monoamine oxidase inhibitors at least 2 weeks before surgery and conversion to a reversible monoamine oxidase inhibitor that should be discontinued 24 hours before surgery. Case reports of the adverse effects of monoamine oxidase inhibitors are plentiful in the literature.

The high risk of withdrawal symptoms with selective serotonergic reuptake inhibitors seems to justify their continuation during surgery. However, the surgical team must be careful to ensure that these patients are not given further serotonin-inducing drugs during anesthesia and postoperative analgesia that can bring on serotonin syndrome. In our experience at Manhattan Eye, Ear and Throat Hospital, we have observed blood pressure lability in the perioperative period, and advocate caution when proceeding with surgery and selective serotonergic reuptake inhibitors and bupropion. During surgery, the surgeon must also maintain meticulous hemostasis given the possibility of increased bleeding with these drugs. Finally, postoperative analgesics such as meperidine and tramadol should be avoided if selective serotonergic reuptake inhibitors are continued perioperatively.

Because of the potential of withdrawal symptoms and emotional lability, we recommend consultation with a psychiatrist for management of these patients when discontinuing the medications discussed above. Discontinuation of propanolol requires the guidance of an internist or cardiologist, but we would advocate that this step be performed 2 weeks before surgery. We have directly observed near fatalities and fatalities when patients have continued this drug in conjunction with intraoperative epinephrine.

Sumatriptan and avitriptan can cause postoperative hypertension, which can be troublesome, particularly in patients undergoing facial surgery. We likewise recommend discontinuing these drugs 2 weeks before elective facial surgery.

First-generation antipsychotics are noted potentiators of sedation, and their use during the perioperative period must be guided by careful administration of anesthetic drugs. Electrocardiograms should be obtained before surgery to look for prolonged QT intervals, and a psychiatrist should be consulted before their continuation during surgery. The use of second-generation antipsychotics during the perioperative period has not been studied sufficiently for a cogent recommendation to be made.

Among herbal medications, St. John's wort has received the most attention with respect to its potential for harm during surgery. This medication should be stopped at least 2 weeks before elective surgery. Ephedra is also noted for its association with myocardial infarction and should be discontinued before surgery as well. Although there is some variation within the literature, most herbs have not been well characterized with respect to surgery. A safe approach, endorsed by the American Society of Anesthesiologists,[3] is to have the patient stop all herbs 2 weeks before surgery, particularly because their efficacy in the treatment of disorders and their adverse effects are not well established in Western medical literature.

CONCLUSIONS

At the Manhattan Eye, Ear and Throat Hospital, growing numbers of cosmetic surgery patients have been noted to be users of antidepressants and herbal medications. The plastic surgeon performing elective aesthetic surgery must keep abreast of the potentially deleterious interactions between these popular medications and perioperative anesthetics.

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