Antidepressants relevant to oral and maxillofacial surgical practice

J. Thomas Lambrecht, Christian Greuter¹, Christian Surber²
Department of Oral Surgery, Oral Radiology and Oral Medicine, School of Dental Medicine, University of Basel, Basel, ¹Department of Orthodontics, University of Bern, Bern, ²Spirig Pharma AG Froschackerstrasse 6, CH-4622 Egerkingen, Switzerland

Address for correspondence:
Dr. J. Thomas Lambrecht, Department of Oral Surgery, Oral Radiology and Oral Medicine, University of Basel, Hebelstrasse 3, CH-4056 Basel, Switzerland.
E-mail: J-Thomas.Lambrecht@unibas.ch

INTRODUCTION

The pharmaceutical industry is constantly developing new active ingredients in order to meet the demands of modern medicine. However, medicines have the potential not only for a specific, desired effect, but also for unwanted side-effects and interactions. Pharmacological interactions are responsible for 3-5% of admissions to hospital every year.[1,2]

The origin of many interactions lies in the pharmacokinetics and specifically the metabolism of the medicines involved. Competition between two active substances for binding to a metabolizing enzyme can lead to competitive inhibition. This can result in increased or toxic plasma concentrations where medicine has a narrow therapeutic range. Conversely, the induction of a metabolizing enzyme by one active substance can reduce the concentration of a second active substance to below the therapeutic range.[3]

The degree of morbidity, the patient’s age, the number of people being treated and the number of medicines prescribed are factors that can influence the incidence of drug interactions. Certain physiological changes occur in old age, which deserve attention when administering medicinal products. With increasing age, there is a decline in the function of the liver and kidneys, organs, which are responsible for the metabolism and excretion of administered drugs.

Furthermore, reduced bodyweight, decreased total body water and an increased percentage of fatty tissue can lead to changes in volumes of distribution.[4] As the population is ageing, the...
number of chronically ill-patients is rising because the probability of suffering from a chronic disease increases with advancing age.\cite{8} The probability and the frequency of undesirable side-effects also increase with the number of drugs being taken concurrently.\cite{5,6,7} As a result of various chronic underlying illnesses, 40% of elderly people take three drugs and 20% even more than five prescription drugs a day.\cite{5,7}

The prevalence of depression is given as 6% in the USA and that of late-life depression just over 13%.\cite{8} The probability of an individual suffering from depression once in his or her lifetime is given as 20-25% for women and 7-12% for men.\cite{9,10} As depressive patients are often treated with medication as well as various therapeutic approaches,\cite{10} these figures correlate closely with the sales figures of prescription drugs. In 1999 and 2000, three and four antidepressants respectively were on the list of the fifty most prescribed medicines in the USA.\cite{6,11} In view of this widespread use, it is therefore not surprising that antidepressants can be involved in pharmacological interactions.

Lack of interest in maintaining oral hygiene in depressed patients is often accompanied by a high-carbohydrate diet and reduced salivation.\cite{8} Several commercially available antidepressants cause the side-effect of xerostomia,\cite{8} which results in a change in the oral flora, reduced self-cleaning of the tissues, a loss of buffer capacity, an increased risk of plaque accumulation, gingivitis, periodontitis, caries, candidiasis and sialadenitis.\cite{12} It is not uncommon for patients to use sweets and sugary drinks to keep the oral mucosa moist and these also contribute to the progression of caries.\cite{13,14} Hyposalivation reduces lubrication of the mucosa, which in turn has an adverse effect on the risk of injury to the oral mucosa and retention of removable dentures. Depressed people therefore often require dental treatment as a consequence of their underlying disease or the pharmacotherapeutic agents they are taking.\cite{8} The aim of this study was to identify frequent adverse drug interactions between antidepressants and medications commonly administered in dentistry in order to give practicing dentists an overview of the scientific literature. A further aim was to highlight the potential risk of drug interactions of different substance groups and where drug interactions are known, to propose safe alternatives within the substance group.

METHODS

The literature review focused on medicines used in dentistry, such as vasoconstrictors in local anesthetics, non-opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antifungals and sedatives from the group of benzodiazepines. The literature search was performed using PubMed, Cochrane and the specific search items. The key words used were “central nervous system agents,” “pharmaceutical preparations,” “drug interactions,” “dental,” “dentist” and the known substance groups in the pharmacological treatment of depression. In addition, the medical and dental libraries of the Universities of Bern and Basel were searched for studies. The literature review mainly covered trials with patients, which were published between 1984 and 2009. A few significant, older clinical trials or animal experiments from fundamental research were also integrated into the study. The search was repeated several times in order to pick up the latest literature and publications not previously found. Targeted searches for individual pharmaceuticals and their interactions were carried out.

RESULTS

Interactions with vasoconstrictors

The administration of vasoconstrictors as an additive to local anesthetics (adrenaline, noradrenaline, α-methyl noradrenaline, isoprenaline and phentylephrine) during antidepressant treatment with tricyclic antidepressants (TCAs) [Table 1], bupropion, maprotiline [Table 2] or St. John’s wort [Table 3] can lead to adverse drug interactions, which manifest themselves as an increase in the effect of the vasoconstrictors on the circulatory system.

The pressure rise during administration of a TCA is due to inhibition of neuronal reuptake of the vasoconstrictor. Intravenous administration of adrenaline or noradrenaline to healthy subjects led to a two- to eight-fold increase in the pressure response to the vasoconstrictor.\cite{2,19} The serious hypertensive reaction can cause symptoms such as severe headaches and vomiting.\cite{17} The patients should therefore be carefully monitored for signs of hypertension or sympathomimetic effects.\cite{38} The interaction between TCAs and adrenaline is a known interaction, which can follow a potentially life-threatening course and can cause permanent damage.\cite{2,19}

Friedlander and Bril\cite{18} and Friedlander et al.\cite{24} discussed the clinical relevance of this reported hypertensive reaction because various other authors were unable to find such a reaction. The complete absence of case studies in the English-language scientific literature at least calls into question the drug interaction between vasoconstrictors in local anesthetics and TCAs.\cite{37} In view of possible variations between different species, Brown\cite{20} challenged the recommended maximum dose of the vasoconstrictor adrenaline, which was derived from an animal experiment with dogs\cite{21} without being able to draw on results of any study in human subjects.

Certain authors have argued that the administration of a TCA over a prolonged period at best causes desensitization to vasoconstrictors and therefore might reduce the risk of the interaction.\cite{12,19} TCAs block the alpha-adrenergic receptors, which are responsible for vasoconstriction in the smooth musculature. The usual vasoconstriction caused by adrenaline is thereby reduced. Instead, adrenaline activates the beta-adrenergic receptors, which trigger a vasodilatory effect. The consequences can be hypotension and tachycardia. Blood flow at the injection site increases so that a larger quantity of the local anesthetic enters the bloodstream. The risk of systemic toxicity rises while the duration of local anesthesia is shortened.\cite{13,42} When adrenaline-impregnated retraction cords are used, a large amount of adrenaline can quickly be absorbed through the periodontium and the adjacent tissue.\cite{2,24}

The role of the catecholamines adrenaline, noradrenaline and α-methyl noradrenaline in terms of drug interactions with monoamine oxidase inhibitors (MAOIs) is a matter of some controversy [Table 4]. Various authors do not expect any interaction between MAOIs and the catecholamines because catecholamines are not primarily degraded by monoamine oxidase but are mainly methylated by the enzyme catechol-O-methyltransferase.\cite{28,19,24,47} Back in 1971, Barar et al.\cite{25} found no blood pressure increase in subjects pre-medicated with MAOI after intravenous infusion of adrenaline or noradrenaline. Inhibition of the enzyme monoamine oxidase,
which is responsible for the degradation of indirectly active and mixed-action sympathomimetics, thus does not cause a significant rise in the concentration or duration of action of the directly active dental vasoconstrictor.\textsuperscript{136}

**Interactions with non-opioid analgesics (paracetamol)**

The co-administration of paracetamol reduces the metabolism of TCAs and their heterocyclic derivatives,\textsuperscript{10,11,12,48} which can increase the concentration and hence the risk of possible toxicity of the antidepressant.\textsuperscript{136} Paracetamol should therefore be used with caution in combination with TCAs.\textsuperscript{108}

The induction of cytochrome (CYP) 1A2 by St. John’s wort and carbamazepine, as a result of increased metabolism, leads to reduced efficacy of paracetamol\textsuperscript{22,47,49,50} and to accumulation of metabolites.\textsuperscript{147} The accumulation of metabolites can increase the risk of hepatotoxicity developing during long-term use.\textsuperscript{147,51,52} The possibility of greater hepatotoxicity caused the Food and Drug Administration to advise against a combination of kava (snuff) and paracetamol at high doses and over a prolonged period.\textsuperscript{131}

**Interactions with NSAIDs**

However, owing to the increased serum level of lithium, there is also a stronger possibility of lithium intoxication,\textsuperscript{8} which can occur after only 5–10 days during treatment with NSAIDs\textsuperscript{147} [Table 5]. After withdrawal of the selective cyclooxygenase inhibitors rofecoxib and celecoxib, the serum levels of lithium return to a normal level. At the same time, the symptoms of lithium toxicity disappear.\textsuperscript{136}

Aspirin can displace valproate from protein binding\textsuperscript{131} and by inhibiting the metabolism,\textsuperscript{11,52} lead to elevated serum levels of valproate.\textsuperscript{131} The administration of aspirin or other NSAIDs in combination with valproate, carbamazepine and selective serotonin reuptake inhibitors (SSRIs) can cause excessive bleeding.\textsuperscript{11,51,58,54,59} Weinrieb et al.\textsuperscript{62} reported the synergistic interaction in a man, which led to fatal gastrointestinal bleeding because of severe liver damage (cirrhosis of the liver, esophageal varices, thrombocytopenia), hypertension and co-administration of aspirin and metoprolol (SSRI).

Clark\textsuperscript{432} recommended more frequent monitoring of serum lithium levels when administering NSAIDs in addition to existing lithium therapy. However, short-term concurrent use of NSAIDs and lithium or SSRIs for 2–3 days appears to be justifiable in healthy subjects.\textsuperscript{147} Co-administration of NSAIDs to patients who are known to be taking SSRIs should be undertaken with caution\textsuperscript{132,60} and only under careful supervision.\textsuperscript{62} Elderly patients with known gastrointestinal ulcers or bleeding who are receiving SSRI therapy should refrain from using NSAIDs.\textsuperscript{147}

Various authors recommend doing without NSAIDs in general when patients are concurrently receiving drug treatment with lithium, valproate and SSRIs\textsuperscript{51,36,22,58,43} and replacing them with paracetamol\textsuperscript{58,29} or narcotic analgesics.\textsuperscript{123,10,58,29}

**Interactions with antibiotics**

**Macrolide antibiotics and fluoroquinolones**

The macrolide antibiotics erythromycin and clarithromycin, by inhibition of the isoenzymes CYP 3A4 and CYP 1A2,\textsuperscript{131} influence

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**Table 1: Possible interactions with vasoconstrictors and TCAs**

| Antidepressant | Possible interactions with vasoconstrictors and TCAs | References |
|---------------|---------------------------------------------------|------------|
| TCAs          | Transient potentiated sympathomimetic activity     | 15-18,12   |
|               | Increase in systolic blood pressure                 | 19,8,20,2  |
|               | Significant increase in arterial and central venous pressures | 21,9,22 |
|               | Disturbances of cardiac rhythm                      | 23,17,19,11,24,9,8,20,22 |
|               | Delayed cardiac conduction                          | 9         |
|               | Serious hypertension                                | 25-27,21,23,15,28,29,17,19,30,11,24-31,33,8,18,10,34,12 |
|               | Serious respiratory depression, arrhythmias, cardiotoxicity, death | 15      |

TCAs = Tricyclic antidepressants

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**Table 2: Possible interactions with vasoconstrictors and maprotiline, bupropion**

| Antidepressant | Possible interactions with vasoconstrictors and maprotiline, bupropion | References |
|---------------|------------------------------------------------------------------------|------------|
| Maprotiline   | Increase in mean arterial and central venous pressure due to adrenaline and especially $\alpha$-methyladrenaline | 21         |
| Bupropion     | Serious hypertensive reaction                                           | 21,33      |

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**Table 3: Possible interactions with vasoconstrictors and St. John’s wort**

| Antidepressant | Possible interactions with vasoconstrictors and St. John’s wort | References |
|---------------|------------------------------------------------------------------|------------|
| St. John’s wort | Prolonged action of adrenaline and $\alpha$-methyladrenaline   | 36         |
|               | Increased, prolonged rise in heart rate and increased cardiac contractility due to adrenaline—higher risk of arrhythmias | 36         |
|               | Hypertension as a consequence of prolongation of peripheral vascular resistance due to adrenaline and especially $\alpha$-methyladrenaline | 36         |

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**Table 4: Possible interactions with vasoconstrictors and monoamine oxidase inhibitors**

| Antidepressant Effect | Possible interactions with vasoconstrictors and MAOIs | References |
|-----------------------|------------------------------------------------------|------------|
| MAOIs                 | Potentiation/ hypertension Possible potentiation of sympathomimetic effects of vasoconstrictors | 17,43,7    |
|                       | Hypertension with possible myocardial infarction or cerebrovascular accident | 12,36,27,7,44,55 |
|                       | No interaction No clinically relevant Interaction | 23,28,46,19,30,38,24,31,8,47,2 |

MAOIs = Monoamine oxidase inhibitors

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References

- Lambrecht, et al.: Antidepressants relevant to maxillofacial practice
- Various authors recommend doing without NSAIDs in general when patients are concurrently receiving drug treatment with lithium, valproate and SSRIs and replacing them with paracetamol or narcotic analgesics.
- Clark recommended more frequent monitoring of serum lithium levels when administering NSAIDs in addition to existing lithium therapy.
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- Various authors recommend doing without NSAIDs in general when patients are concurrently receiving drug treatment with lithium, valproate and SSRIs and replacing them with paracetamol or narcotic analgesics.
- Clark recommended more frequent monitoring of serum lithium levels when administering NSAIDs in addition to existing lithium therapy.
the hepatic metabolism of a large number of medicines, which can intensify their effects\[8,11\] [Table 6].

In the case of TCAs and SSRIs, combination with erythromycin or ciprofloxacin (fluoroquinolone) can cause an accumulation of substrate, resulting in excessive, anticholinergic and α1-blocking activity. Possible consequences are xerostomia, constipation, increased intraocular pressure, tachycardia, dysrhythmias, confusion and orthostatic hypotension.\[22\]

An interaction is highly improbable when erythromycin is administered for the purpose of endocarditis prophylaxis.[28,29,64] Erythromycin should be administered with caution, the patients should be closely monitored 29 and the dose of the drugs administered should be reduced.[14,48,65,66] It is advisable to replace erythromycin with dirithromycin or azithromycin because these antibiotics do not influence the hepatic metabolism of other drugs by inhibition of the CYP isoenzymes.\[6,11\]

**Tetracyclines and metronidazole**

Tetracyclines and metronidazole reduce the renal clearance of lithium, which can lead to an increased serum level of lithium\[14,42,55\] and the onset of lithium toxicity involving confusion, ataxia and renal damage. The drug interaction with metronidazole was described in three well-documented case reports.[67] However, a clinical trial with tetracycline failed to confirm the described case report[48] and even showed a slight fall in the blood concentration of lithium during co-administration of tetracycline.\[67\] When lithium is being taken concurrently, the use of metronidazole should be avoided[67] and an alternative antibiotic should be used instead.\[14\] The photosensitivity of tetracycline can be increased by added pharmacodynamic effects of St. John’s wort in certain patients.[10,22,51] The metabolism of doxycycline is accelerated by carbamazepine[55,59] and consequently the effectiveness of the antibiotic is reduced.\[14\]

**Interactions with antifungals (triazole derivatives)**

Induction of the metabolizing CYP 3A4 isozyme by St. John’s wort can reduce the efficacy of ketoconazole.[5,50] Conversely, ketoconazole, fluconazole, itraconazole and terbinafine themselves are potent inhibitors of the CYP 3A4 isozyme, which is responsible for the metabolism of TCAs,[3] trazodone[20] and carbamazepine.[10,22,31,67] As a consequence, the plasma concentrations of TCAs and carbamazepine may rise and reach toxic levels.\[10,22,31,67,71\] Raised serum levels of carbamazepine pose an increased risk of ataxia, dizziness, drowsiness and confusion occurring.\[22,67,63\] The interaction of carbamazepine with fluconazole was described in two case reports.[63] In addition, fluconazole can further intensify the inhibition of platelet aggregation by valproate, which can result in pronounced bleeding.\[67\]

**Interactions with benzodiazepines**

Drug interactions must be anticipated when benzodiazepines are administered during treatment with a majority of common antidepressants [Table 7]. The hepatic metabolism of benzodiazepines can be increased by inducers of the CYP 3A4 isozyme.[22,79,82] By this route, carbamazepine and St. John’s wort cause a reduction of the plasma concentration of benzodiazepines and hence reduced sedation.[22,32,50,79,83] However, the clinical

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**Table 5: Possible interactions with NSAIDs and antidepressants**

| Antidepressants | Interaction with | Mechanism | Consequences | References |
|-----------------|-----------------|-----------|--------------|------------|
| Lithium         | NSAIDs          | Renal excretion of lithium is reduced by NSAIDs | Raised serum level of lithium | 1,28,45,14,54,55,11,42,56,10,5,36,22 |
| Valproate       | Aspirin         | Inhibition of platelet aggregation increased by valproate | Excessive bleeding | 57,51,58,54,55,59 |
| Carbamazepine   | NSAIDs          | Reduction of serotonin receptors at the platelet surface | Increased risk of gastrointestinal bleeding | 54,59 |
| SSRIs           | Aspirin         | Reduction of serotonin receptors at the platelet surface, reduction of platelet binding affinity and of secretion of platelets in response to collagen, blockade of calcium mobilization in the platelets | Severely (3 to 12-fold) | 60,22,12,61 |
|                 | NSAIDs          | Increased risk of gastrointestinal bleeding | Increased risk of gastrointestinal bleeding | 60,22,12,61 |

NSAIDs = Non-steroidal anti-inflammatory drugs, SSRIs = Selective serotonin reuptake inhibitors

**Table 6: Possible interactions with macrolide antibiotics and antidepressants**

| Macrolide     | Antidepressants | Mechanism | Consequences | References |
|---------------|-----------------|-----------|--------------|------------|
| Erythromycin  | Heterocyclic derivatives | Reduction of antibiotic effect via induction of the metabolizing CYP 3A4 | Increased probability of side effects, possible | 33,10 |
|               | St. John’s wort  | Increased serum level of lithium | Toxicity of antidepressants | 45,10,63 |
|               | Lithium         | Increased serum levels of antidepressants because of inhibition of hepatic metabolism | 14,54,47 |
|               | Carbenazepine   | Valproate | 29,28,64,3,57,51,14,54,55,10,59,47,22 |
|               | TCAs            | SSRIs     | 36 |
|               |                 |           | 14,48,54,55,65,66,59,36 |

TCAs = Tricyclic antidepressants, SSRIs = Selective serotonin reuptake inhibitors
significance of interactions with benzodiazepines is probably minimal given their wide therapeutic range.\textsuperscript{34} A few precautions for safe handling of benzodiazepines are mentioned in the literature. When antidepressants such as lithium, TCAs or SSRIs are administered concurrently, benzodiazepines should only be used with the necessary caution.\textsuperscript{8,12,14,20,81}

**DISCUSSION**

In view of the incidence of oral diseases and mental illnesses in our society, dentists in general practice should expect to have to perform time-consuming, demanding and challenging treatments on psychiatric patients.\textsuperscript{105} The selected dental treatment requires not only a higher degree of care and consideration toward the depressed patient, but also a skillful choice of therapeutic agents administered in order to avoid undesirable interactions between medicines.

Detailed history-taking helps to establish the needs and concerns of the patient and create a relationship of trust between the dentist and patient. As much information as possible about the patient’s mental and physical state of health should be gained from this first discussion. The patient’s medication history plays a key role in this process, as a means of obtaining a complete list of all medicines the patient has consumed. Any possible substance misuse should also be recorded as well as any herbal or homoeopathic remedies, prescription drugs and over-the-counter medicines. The dentist should adopt a helpful, unprejudiced attitude because the stigmatization about psychiatric illness in our society might cause a lot of patients to conceal their depression. It should be made clear to the patient that the information gathered will be treated confidentially and is an essential requirement for safe dental treatment.\textsuperscript{88}

The over-65 age group will make up 20% of the total population by 2030 as a result of demographic trends. The group aged over 85 years will actually double by comparison with today.\textsuperscript{102} The probability of a drug interaction occurring in dental practice will rise further in the future because the high prevalence of late-life depression, the increase in the number of chronically ill, multiple drug consumption and physiological changes in old age are major contributory factors.

The constant growth in preventive and non-prescription natural remedies consumed in the last two decades requires the practicing dentist to be increasingly vigilant. This is because most consumers are unaware that natural remedies such as St. John’s wort can also in the literature about the possible drug interactions with antidepressants. These conflicting statements are partly historical in origin and partly due to older publications being uncritically quoted. However, there is an absence of detailed, broadly based studies on the subject of drug interactions in the area of dental and antidepressant pharmaceuticals, which could be used to clarify the situation. Furthermore, strikingly few case reports of drug interactions in dental practice have been published. Hence, it seems that many of the possible interactions do not present pressing clinical problems. In the literature published in English, there are no case reports of the described interaction between TCAs and adrenaline or other vasoconstrictors. One possible reason for the lack of case studies might be that the interactions are not always obvious to the dental practitioner and cannot clearly be interpreted as drug interactions. Pharmacological interactions can follow a silent course in young patients while the same interaction in an adult can cause a severe drug interaction.\textsuperscript{121} Accidental intravasal administration of local anesthetics with vasoactive substances can also trigger similar symptoms to a drug interaction. The adverse drug interaction might quite generally overwhelm the people involved. A possible medical emergency might stretch the dentist to his diagnostic limitations. On the other hand, the patient might be embarrassed or even feel unsettled by the necessary additional care and attention from the dental team. The small number of published case reports does, however, suggest a very low incidence of drug interactions in dental practice.

Adverse drug interactions should always be anticipated whenever several pharmacological therapeutic agents are being administered. As a general finding of this study, the older antidepressants such as TCAs and MAOIs showed higher potential for drug interactions (see recommendation) [Table 8] than newer drugs from the group of SSRIs and other agents with a specific mechanism of action.\textsuperscript{102} In other words, the more specific the action of the chosen antidepressant (on a receptor, for instance), the safer its co-administration with other drugs seems to be. However, comprehensive studies and problem-free everyday use of the newer antidepressants are needed to further reinforce these statements.

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**Table 7: Possible interactions with benzodiazepines and antidepressants**

| Antidepressant | Interaction | Other interactions | Mechanism | References |
|---------------|------------|--------------------|-----------|------------|
| Lithium       | Increased sedation | Hypothermia, Psychotic episodes | Influence on the appropriate degradation by inhibition of CYP 3A4 | 27,14,54,55 |
| Valproate     |            | Increased serum level and prolonged half-life of benzodiazepines, psychomotor impairment | Influence on appropriate degradation by inhibition of CYP 3A4 | 72,32 |
| Nefazodone    |            |                    | Influence on appropriate degradation by inhibition of the metabolizing CYP isoenzymes (CYP 3A4, CYP 2C9, CYP 2C19, CYP 2D6) | 73,70,74,75,63,36 |
| SSRIs         |            |                    |           | 76-78,74,32,14,48,54,55,33,10,63,36,47 |
| TCAs          | Increased toxicity of antidepressants, undesirable respiratory depression, orthostatic hypotension | | | 13,39,26,27,21,16,72,17,45,20,33,10,12 |
| MAOIs         | Intensified effect and increased toxicity of antidepressants, hypertensive crises | | | 26,27,45 |
| Kava          | Coma       |                    |           | 69,79 |

TCAs = Tricyclic antidepressants, MAOIs = Monoamine oxidase inhibitors
cause side effects, and around 70% of patients fail to mention their use of natural medicines to their dentist.\(^7\)\(^9\)

In the case of patients with a high risk of a drug interaction, for instance elderly patients and/or patients with underlying medical conditions, the pharmaceuticals being used should be chosen with great care. The use of safe alternatives to certain drugs can help to prevent potentially dangerous interactions. Accurate and careful medical and pharmacological history-taking are a basic prerequisite for the identification of possible sources of risk. Consultation with all the attending physicians involved is always advisable as a precaution before any drug is administered to at-risk patients. Specific inquiry about possible interactions is strongly recommended if there is any uncertainty about the drugs being administered, especially in at-risk patients who are taking a large number of medicines and have the relevant general medical problems. The constant growth in knowledge about the CYP P450 isoenzymes, which are responsible for the metabolism of a majority of drugs, will help to simplify the identification of possible interactions in the future.

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