

TABLE 3

ADVERSE DRUG INTERACTIONS IN DENTISTRY INVOLVING ANALGESICS USED FOR A PERIOD OF LESS THAN FIVE DAYS.

DRUG INTERACTION	SIGNIFICANCE RATING*	CLINICAL IMPLICATIONS
Nonsteroidal Anti-inflammatory Drugs[†]		
NSAIDs and certain antihypertensives: angiotensin-converting enzyme inhibitors, diuretics, β -blockers (interaction does not apply to calcium-channel blockers)	4	An NSAID may be coprescribed if required for four days or less. Coadministration should be avoided in patients with severe congestive heart disease. Should be combined cautiously in elderly or black patients.
NSAIDs and lithium	2	Toxicity may result; however, evidence is not clear at the present time. Combination should be avoided, or NSAIDs should be prescribed for very short term. Use with elderly patients should be avoided.
NSAIDs and anticoagulants	2	Gastrointestinal bleeding may result. Combination should be avoided. High-dosage aspirin (more than 3 grams per day) is rated 1.
NSAIDs and methotrexate	1	Toxicity may result. Combination with high-dosage methotrexate, as used for cancer therapy, should be avoided. Low-dosage methotrexate, as used for arthritis, is of little concern.
NSAIDs and alcohol	2	Predisposes patient to gastrointestinal bleeding. Combination should be avoided.
NSAIDs and digoxin	2	Toxicity may result. Combination should be avoided if patient is elderly or has renal disease; less concern is necessary if patient's renal function is normal.
NSAIDs and cyclosporine	4	Toxicity may result. Combination should be avoided if possible.
NSAIDs and other NSAIDs, acetaminophen	5	Renal damage may result when given long term. Combination should be avoided if possible.
Aspirin and oral hypoglycemics	2	Hypoglycemic effect may be increased. Combination should be avoided.
Aspirin and anticonvulsants	4	Toxicity may result with valproic acid. Combination should be avoided if possible.
Aspirin and carbonic anhydrase inhibitors	3	Toxicity may result. Combination should be avoided if possible.

* This rating system was described previously.¹⁰ See Table 2.
[†] The considerations listed for NSAIDs include aspirin.

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tion is four days or less.⁹

Using the system introduced in the original article in this series,¹⁰ which is shown in Table 2, this interaction may be rated

as follows. For long-term use, the severity of the interaction is moderate and the documentation indicates that it is probable, which would lead to a sig-

nificance rating of 2. When we assess short-term use of the NSAIDs common in dentistry (Table 1), the documentation indicates that the interaction is,

TABLE 3 (CONTINUED)

ADVERSE DRUG INTERACTIONS IN DENTISTRY INVOLVING ANALGESICS USED FOR A PERIOD OF LESS THAN FIVE DAYS.		
DRUG INTERACTION	SIGNIFICANCE RATING*	CLINICAL IMPLICATIONS
Acetaminophen		
Acetaminophen and alcohol Acute alcohol ingestion	5	Combination may be used if patient has a healthy liver. In alcoholics, or those with liver disease, lower maximum dosage (less than 4 g/day) should be used.
Cessation of alcohol ingestion after chronic intake	1	Liver damage may result. Alcoholic patients should not be told to stop drinking if acetaminophen is used.
Opioids and alcohol	2	Additive sedation may result. Combination should be avoided.
Meperidine and monoamine oxidase inhibitors, or MAOIs	1	Toxicity may result. Combination should be avoided if patient has taken MAOI in past 14 days.

* This rating system was described previously.¹⁰ See Table 2.

at most, possible. Therefore, in our context, a significance rating of 4 is most appropriate.

In conclusion, it appears that we still can safely prescribe NSAIDs for a short duration to patients taking antihypertensives. Possible exceptions are those who are most susceptible to this interaction: patients who are elderly, have severe congestive heart failure or have low concentrations of renin. In these cases, use of acetaminophen is most appropriate.

NSAIDs and lithium.

Lithium therapy is the treatment of choice for patients with bipolar depression. This drug is associated with a low therapeutic index; that is, the effective dose is close to the toxic dose. Adverse effects of excessive lithium concentrations include polyuria, polydipsia, nausea, vomiting, diarrhea, tremors and sedation. Even higher concentrations can lead to convulsions, coma and death.

It has been suggested that

NSAIDs increase the serum concentration of lithium and thereby predispose the patient to toxicity. The mechanism is not known with certainty, but it may involve inhibition of renal prostaglandins that leads to increased lithium reabsorption, which is relevant because lithium is excreted primarily by the kidneys.^{11,12} This proposed interaction is described in a number of case reports and small clinical trials. Indomethacin is reported to have the greatest effect, whereas sulindac and aspirin do not alter lithium levels.^{13,14} Two studies have implicated ibuprofen and naproxen, two drugs used in dentistry.^{13,15} It must be pointed out that these latter studies were small, with sample sizes of nine and seven, respectively. Furthermore, they involved only older patients, and there was great interindividual variability in the measured lithium levels. In addition, the researchers did not

assess patients until three days after NSAID administration. The accumulation of these factors should lead to a reconsideration of the validity of this interaction. It may occur in specific population groups such as elderly people, but the evidence for a general recommendation is weak. Given the lack of rigorous evidence supporting the interaction, it is tempting to ignore it, except for lithium's low therapeutic index. If the interaction truly exists, the consequences are serious. Clearly, more study is needed before definitive recommendations can be made.

This NSAID-lithium interaction has the potential to be severe in susceptible people taking lithium. It is not clear who is predisposed to this interaction, but elderly people likely are involved. In terms of the quality of the documentation, it seems equivocal whether this interaction should be rated as suspected, because there are