Assessment of Salsalate, a Nonacetylated Salicylate, in the Treatment of Patients with Arthritis

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ABSTRACT

This study evaluated physicians' use of the occurrence of tinnitus as a tool to establish the optimal dosage of salsalate, a nonacetylated salicylate, in patients with arthritis treated in routine clinical practice. The use of printed educational materials to improve compliance was also studied prospectively. A total of 782 patients were enrolled in this 3-week study by 95 general practitioners in an office setting. Of the 771 assessable patients, 90.0% had osteoarthritis, 9.7% had rheumatoid arthritis, and 0.3% had both types of arthritis. Most patients experienced improvement of symptoms after 3 weeks of treatment. There were no differences in the rates of improvement at the first and third weeks of treatment between patients with osteoarthritis and patients with rheumatoid arthritis. In addition, duration of arthritis had no effect on rates of improvement. Rates of patient satisfaction tended to increase over the study period. Rates of patient satisfaction did not differ significantly at the first and third weeks between patients who did receive printed educational materials and those who did not. Treatment was discontinued in 234 patients (30.4%) because of side effects. The most frequent reasons for discontinuation were gastrointestinal symptoms (n = 102; 13.2%) and tinnitus (n = 52; 6.7%). The clinical effectiveness and safety of salsalate were confirmed in patients with arthritis in routine clinical practice settings.

INTRODUCTION

Patient compliance in following a prescribed medication regimen and patient satisfaction with the regimen are important factors in successful treatment of a condition. The literature reports an incidence of noncompliance of 30% to 80%, with a variety of factors having an impact on this incidence.[1] Attaining compliance has been shown to be more difficult in long-term, chronic diseases such as arthritis, where the need for proper medication, exercise, and diet continues for a lifetime. It is also more difficult for patients to adhere to a

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regimen if their improvement is either gradual or delayed, as it is in arthritis.

To understand noncompliance and patient satisfaction with a particular therapy requires evaluation of at least the following factors: patient characteristics (age, race, and sex); particularly bothersome side effects; lack of sufficient efficacy of the medication; frequency of dosing regimen; characteristics of the disease; patient perception of response to the medication; and, importantly, lack of proper patient education/instruction.[2] Although it is commonly thought that providing written instructions to patients has an impact on compliance, few data exist to document this effect.[3]

Results of several clinical studies[4–9] suggest that acetylated salicylates, nonacetylated salicylates, and other nonsteroidal anti-inflammatory drugs (NSAIDs) produce comparable therapeutic responses in patients with osteoarthritis and rheumatoid arthritis. In addition, salicylates may cause tinnitus, which is generally recognized to be dose related.[10] However, it has been demonstrated that nonacetylated salicylates have less of an effect than acetylated salicylates and other NSAIDs on prostaglandin inhibition; thus they have fewer effects on the gastrointestinal (GI) mucosal barrier, renal function, and platelet aggregation, and cause significantly fewer ulcers/erosions and less occult GI blood loss.[11,12]

The usual daily maintenance dose for treatment of osteoarthritis and rheumatoid arthritis is 3.6 g for acetylated salicylate and 3 g for nonacetylated salicylate.[13] In general, the effective dose of these agents may be reached by titrating upward until tinnitus occurs, then lowering the dose slightly until tinnitus disappears but clinical improvement is maintained.

The objectives of this study were to prospectively evaluate physician use of the occurrence of tinnitus as a tool to establish the optimal dosage of salsalate,* a nonacetylated salicylate, in the treatment of patients with arthritis who are seen in routine practice settings; to prospectively evaluate patient satisfaction through the use of printed educational materials; and to further delineate the short-term efficacy and safety of salsalate.

PATIENTS AND METHODS

This study was an open-label, multicenter, prospective evaluation conducted throughout Canada. The study was approved by an independent Canadian institutional review board, and each patient gave written informed consent before initiation of therapy.

A total of 95 general practitioners from 9 of 10 provinces participated in the study. Each participating physician was provided with a program kit containing the study protocol, patient consent forms, sufficient medication to treat 10 patients with salsalate for 25 days (ie, 10 bottles each containing one hundred 750-mg salsalate tablets), and sequentially numbered clinical evaluation cards (1 per patient). Patients were provided with enough medication for 25 days in case their appointments were delayed. In addition, 50% of the program kits contained, on a randomized basis, a patient brochure, "Managing Your Arthritis," produced with the technical assistance of The Arthritis Society. The brochure included a discussion of the need for compliance and explained the relation-

*Trademark: Disalcid™ (3M Pharmaceuticals, London, Ontario, Canada).

ship of tinnitus to the effect of salicylate and dosage adjustment.

Men and nonpregnant, nonlactating women of at least 18 years of age were included in the study. Eligible patients were to have had a clinical diagnosis of rheumatoid arthritis as defined by the American Rheumatism Association[14] or symptomatic osteoarthritis. Excluded were those patients who were intolerant of salicylates, taking another NSAID within 24 hours of beginning salsalate therapy, or having symptoms of a GI disorder. Also excluded were patients with colitis, known preexisting bleeding disorders, or known hearing loss, and patients currently experiencing tinnitus. The duration of the study was 3 weeks.

Patient evaluation, recording of medical history, and a pertinent physical examination were conducted at the initial visit, and then salsalate, in 750-mg tablets, was prescribed at a dose of 1500 mg (2 tablets) twice daily. Follow-up visits occurred at 1, 2, and 3 weeks after initiation of salsalate therapy. For each patient, the physician indicated on the clinical evaluation card an assessment of the degree of patient improvement (ie, marked, moderate, mild, none, or deterioration of symptoms) and patient satisfaction with the prescribed therapy (excellent, good, fair, or poor). All adverse experiences, including tinnitus, were reported on the clinical evaluation card and graded by the physician in terms of possible relationship to salsalate administration.

The current dosage of salsalate was recorded and dosage adjustments were made by the physician using the following criteria: (1) If salsalate was judged to be clinically effective and there was no evidence of bothersome tinnitus, hearing loss, or side effects requiring discontinuation, the dose remained the same (ie, 2 tablets twice daily); (2) If salsalate was judged to be clinically effective but its use was restricted by side effects or by bothersome tinnitus, the dose was reduced by 1 tablet (750 mg) daily (reduction of either the morning dose by 1 tablet or the evening dose by 1 tablet); (3) If salsalate was judged to be not clinically effective and there was no evidence of tinnitus, hearing loss, or other side effects requiring discontinuation, the dose was increased by 1 tablet daily (increase of either the morning dose by 1 tablet or the evening dose by 1 tablet); (4) If salsalate was judged to be not clinically effective and there were side effects or bothersome tinnitus, the drug was discontinued with side effects noted on the clinical evaluation card.

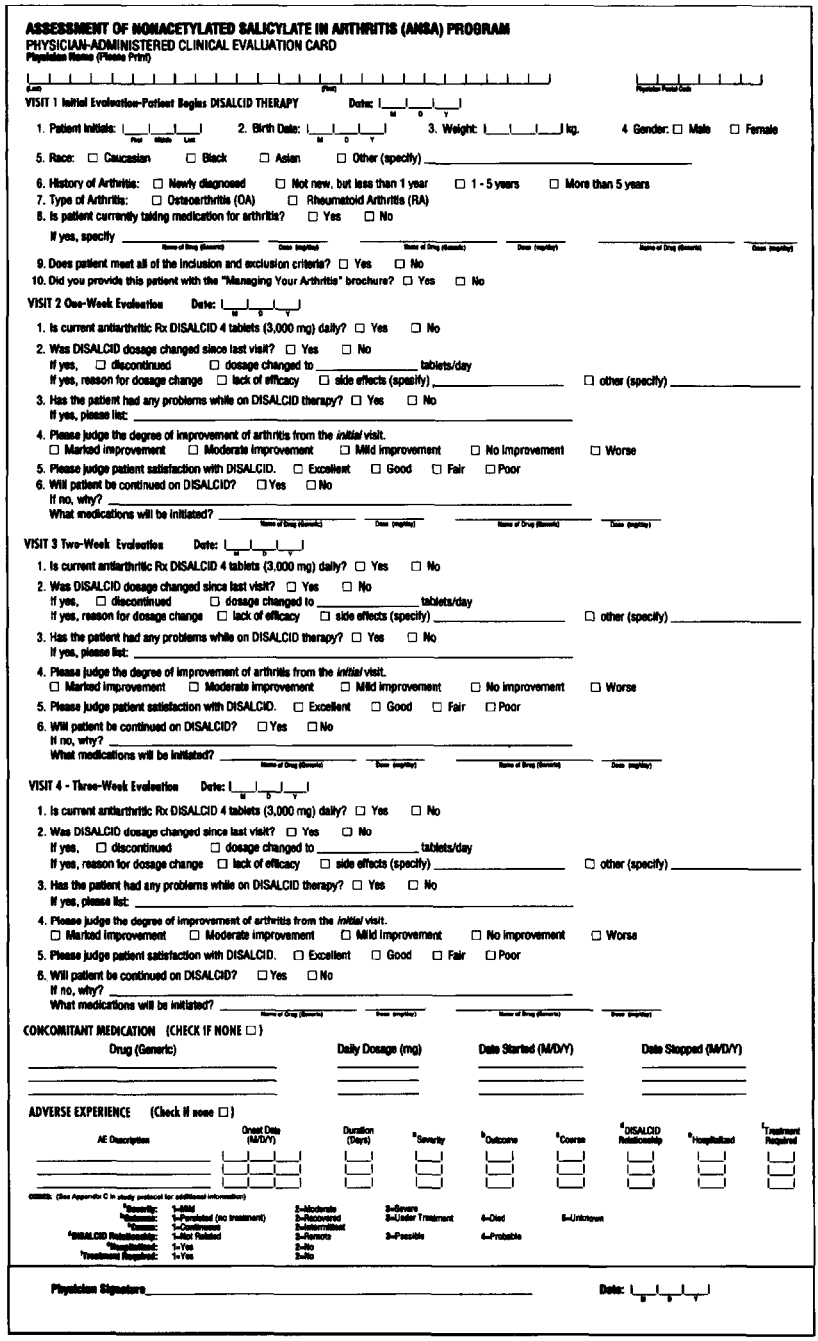
A minimum of 5 days had to elapse between upward adjustments to permit proper evaluation of response. The dose (not to exceed 6 tablets or 4500 mg per day) was to be adjusted upward to enhance efficacy or downward to minimize side effects. Dosage adjustments were to be no greater than one 750-mg tablet at a time.

Clinical evaluation cards were to be submitted for each patient after 3 weeks of therapy (Figure 1). Data from the clinical evaluation cards were analyzed using descriptive statistics; associations were evaluated by use of chi-square tests and trends by use of rank scores.[15]

RESULTS

Physician and Patient Demographics

Figure 2 shows the geographic distribution of the 95 physicians who participated in the study. The largest number of physicians participating were from the most populous provinces—Quebec



ASSESSMENT OF NONACETYLATED SALICYLATE IN ARTHRITIS (ANSA) PROGRAM
PHYSICIAN-ADMINISTERED CLINICAL EVALUATION CARD
Physician Name (Please Print)
Last (First) Physician Postal Code

VISIT 1 Initial Evaluation-Patient Begins DISALCID THERAPY Date: M D Y

1. Patient Initials: First Middle Last 2. Birth Date: M D Y 3. Weight: kg. 4 Gender: ☐ Male ☐ Female

5. Race: ☐ Caucasian ☐ Black ☐ Asian ☐ Other (specify) _____

6. History of Arthritis: ☐ Newly diagnosed ☐ Not new, but less than 1 year ☐ 1 - 5 years ☐ More than 5 years
7. Type of Arthritis: ☐ Osteoarthritis (OA) ☐ Rheumatoid Arthritis (RA)
8. Is patient currently taking medication for arthritis? ☐ Yes ☐ No
If yes, specify _____ Name of Drug (Generic) Dose (mg/day) _____ Name of Drug (Generic) Dose (mg/day) _____ Name of Drug (Generic) Dose (mg/day)
9. Does patient meet all of the inclusion and exclusion criteria? ☐ Yes ☐ No
10. Did you provide this patient with the "Managing Your Arthritis" brochure? ☐ Yes ☐ No

VISIT 2 One-Week Evaluation Date: M D Y

1. Is current antiarthritic Rx DISALCID 4 tablets (3,000 mg) daily? ☐ Yes ☐ No
2. Was DISALCID dosage changed since last visit? ☐ Yes ☐ No
If yes, ☐ discontinued ☐ dosage changed to _____ tablets/day
If yes, reason for dosage change ☐ lack of efficacy ☐ side effects (specify) _____ ☐ other (specify) _____
3. Has the patient had any problems while on DISALCID therapy? ☐ Yes ☐ No
If yes, please list: _____
4. Please judge the degree of improvement of arthritis from the *initial* visit.
☐ Marked improvement ☐ Moderate improvement ☐ Mild improvement ☐ No improvement ☐ Worse
5. Please judge patient satisfaction with DISALCID. ☐ Excellent ☐ Good ☐ Fair ☐ Poor
6. Will patient be continued on DISALCID? ☐ Yes ☐ No
If no, why? _____
What medications will be initiated? _____ Name of Drug (Generic) Dose (mg/day) _____ Name of Drug (Generic) Dose (mg/day)

VISIT 3 Two-Week Evaluation Date: M D Y

1. Is current antiarthritic Rx DISALCID 4 tablets (3,000 mg) daily? ☐ Yes ☐ No
2. Was DISALCID dosage changed since last visit? ☐ Yes ☐ No
If yes, ☐ discontinued ☐ dosage changed to _____ tablets/day
If yes, reason for dosage change ☐ lack of efficacy ☐ side effects (specify) _____ ☐ other (specify) _____
3. Has the patient had any problems while on DISALCID therapy? ☐ Yes ☐ No
If yes, please list: _____
4. Please judge the degree of improvement of arthritis from the *initial* visit.
☐ Marked improvement ☐ Moderate improvement ☐ Mild improvement ☐ No improvement ☐ Worse
5. Please judge patient satisfaction with DISALCID. ☐ Excellent ☐ Good ☐ Fair ☐ Poor
6. Will patient be continued on DISALCID? ☐ Yes ☐ No
If no, why? _____
What medications will be initiated? _____ Name of Drug (Generic) Dose (mg/day) _____ Name of Drug (Generic) Dose (mg/day)

VISIT 4 - Three-Week Evaluation Date: M D Y

1. Is current antiarthritic Rx DISALCID 4 tablets (3,000 mg) daily? ☐ Yes ☐ No
2. Was DISALCID dosage changed since last visit? ☐ Yes ☐ No
If yes, ☐ discontinued ☐ dosage changed to _____ tablets/day
If yes, reason for dosage change ☐ lack of efficacy ☐ side effects (specify) _____ ☐ other (specify) _____
3. Has the patient had any problems while on DISALCID therapy? ☐ Yes ☐ No
If yes, please list: _____
4. Please judge the degree of improvement of arthritis from the *initial* visit.
☐ Marked improvement ☐ Moderate improvement ☐ Mild improvement ☐ No improvement ☐ Worse
5. Please judge patient satisfaction with DISALCID. ☐ Excellent ☐ Good ☐ Fair ☐ Poor
6. Will patient be continued on DISALCID? ☐ Yes ☐ No
If no, why? _____
What medications will be initiated? _____ Name of Drug (Generic) Dose (mg/day) _____ Name of Drug (Generic) Dose (mg/day)

CONCOMITANT MEDICATION (CHECK IF NONE ☐)

Drug (Generic)	Daily Dosage (mg)	Date Started (M/D/Y)	Date Stopped (M/D/Y)

ADVERSE EXPERIENCE (Check if none ☐)

AE Description	Onset Date (M/D/Y)	Duration (Days)	[a]Severity	[b]Outcome	[c]Course	[d]DISALCID Relationship	[e]Hospitalized	[f]Treatment Required

CODES: (See Appendix C in study protocol for additional information)

[a]Severity:	1=Mild	2=Moderate	3=Severe		
[b]Outcome:	1=Persisted (no treatment)	2=Recovered	3=Under Treatment	4=Died	5=Unknown
[c]Course:	1=Continuous	2=Intermittent			
[d]DISALCID Relationship:	1=Not Related	2=Remote	3=Possible	4=Probable	
[e]Hospitalized:	1=Yes	2=No			
[f]Treatment Required:	1=Yes	2=No			

Physician Signature _____ Date: D M Y

Figure 1. Clinical evaluation card. Disalcid™ (salsalate) is a trademark of 3M Pharmaceuticals, London, Ontario, Canada.

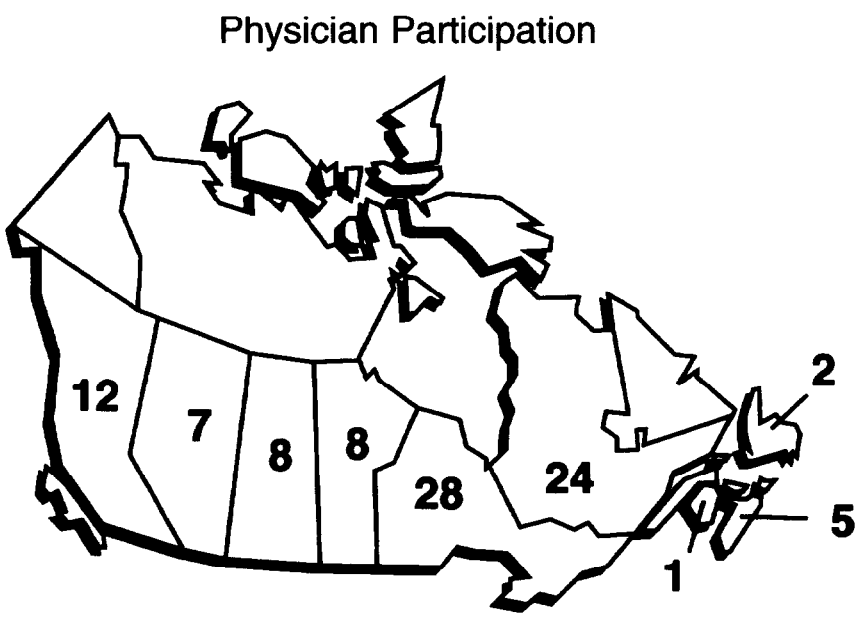


Figure 2. Geographic distribution of the 95 participating physicians.

(25.3%; 24 of 95) and Ontario (29.5%; 28 of 95). A total of 782 patients were enrolled in this study with 9 of 10 provinces represented. As expected, patient distribution closely mirrored that of physicians (Figure 3). Data inconsistencies that could not be reconciled excluded 11 patients from the data analysis. Of the 771 assessable patients, 469 completed the study; 234 were withdrawn because of side effects; 45 were withdrawn because of lack of efficacy; and 23 were withdrawn for other reasons, primarily cost.

As shown in Table I, the mean age of patients was 57 years (range, 19 to 94 years), and there was a slight preponderance of women. Most patients (90.0%) were white. In addition, most patients (90.0%) had osteoarthritis only. The majority (63.0%) of patients evaluated had had their illness for longer than 1 year (29.3%, 1 to 5 years; 33.7%, >5 years) (Figure 4).

Dosing

After the first and third weeks of therapy, there were no significant differences in the mean daily doses of salsalate between patients with osteoarthritis and patients with rheumatoid arthritis (Table II). Minimal dosage adjustment was observed.

Patient Satisfaction

Patients were subdivided into four categories according to duration of illness (Table III). Rates of patient satisfaction (patient response of excellent plus good) did not differ significantly at the first and third weeks among the four duration categories. However, rates of satisfaction increased among all four groups over the study period. Rates of patient satisfaction did not differ significantly at the first and third weeks between patients with osteo-

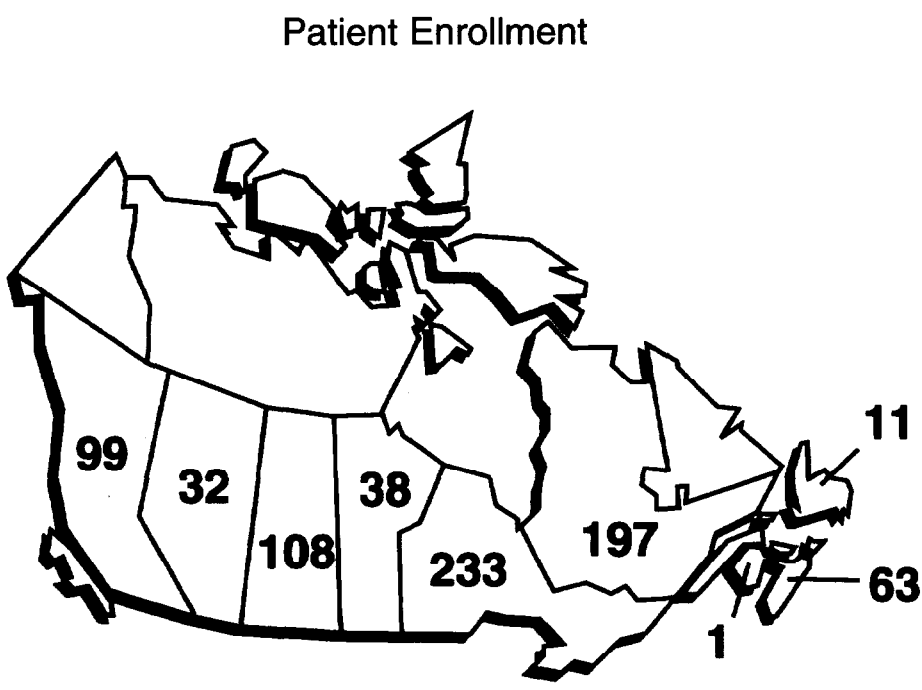


Figure 3. Geographic distribution of patient enrollment.

Table I. Patient demographics (N = 771).

Age (y)	
Mean	57
Range	19–94
Sex (%)	
Female	439 (56.9)
Male	332 (43.1)
Race (%)	
White	694 (90.0)
Oriental	51 (6.6)
Black	11 (1.4)
Other	15 (1.9)
Diagnosis (%)	
Osteoarthritis	694 (90.0)
Rheumatoid arthritis	75 (9.7)
Osteoarthritis and rheumatoid arthritis	2 (0.3)

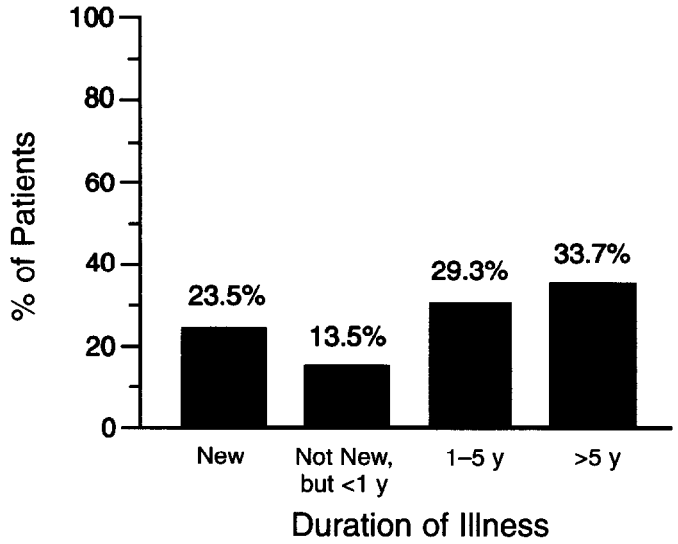


Figure 4. Percentage of patients according to disease duration.

arthritis and those with rheumatoid arthritis (first week—chi-square = 1.516, P = 0.2182; third week—chi-square = 0.104, P = 0.750). Rates of satisfaction tended to increase in both groups of patients over the course of the study, particularly in patients with rheumatoid arthritis (Table IV). Rates of patient satisfaction did not differ significantly at the first and third weeks between patients who did receive the brochure "Managing Your Arthritis" and those who did not (first week—chi-square = 0.913, P = 0.339; third week—chi-square = 0.002, P = 0.962) (Table V).

Side Effects

A total of 324 patients experienced one or more side effects. The most common were GI disorders, tinnitus, and dizziness. Treatment was discontinued in 234 patients (30.4%) because of side effects judged by physicians as possibly or probably related to therapy; 102 patients (13.2%) had GI side effects, 52 patients (6.7%) had tinnitus, 13 patients (1.7%) had dizziness, and 67 for various other reasons. There was no dose adjustment in these patients prior to discontinuation.

Concomitant Medications

A total of 25% of patients received concomitant medications during the study; acetaminophen was the most commonly prescribed medication. Less than 2% of patients received concomitant cytoprotective agents during the study, in contrast to a reported incidence of 10% to 20% with other NSAIDs.[16]

DISCUSSION

In the past, most of the data on salsalate have been gathered within the confines of tightly controlled clinical trials that dic-

Table II. Mean daily dose of salsalate at weeks 1 and 3 in patients with osteoarthritis and patients with rheumatoid arthritis (N = 771).

Type of Arthritis	Mean Daily Dose (mg)
Osteoarthritis	
Week 1	2904
Week 3	2971
Rheumatoid arthritis	
Week 1	2943
Week 3	2882

Table III. Rates of patient satisfaction (excellent plus good) at weeks 1 and 3 according to disease duration (N = 771).*

Duration	Satisfaction (excellent plus good)
Newly diagnosed (%)	
Week 1	83/178 (46.6)
Week 3	113/140 (80.7)
Not new, but <1 y (%)	
Week 1	58/102 (56.9)
Week 3	73/93 (78.5)
1–5 y (%)	
Week 1	129/218 (59.2)
Week 3	151/188 (80.3)
>5 y (%)	
Week 1	106/249 (42.6)
Week 3	121/180 (67.2)

*Patient numbers vary because patients were withdrawn throughout the study.

tated dosing schedules and greatly restricted the clinicians' ability to treat patients individually. Previous studies[4–11] have evaluated the efficacy and decreased potential for upper GI erosions and ulcerations. This study allowed a more flexible dosing regimen and examined the physicians' use of the occurrence of tinnitus as a therapeutic monitoring tool to determine optimal dosing. There was little evidence to support this practice because minimal dosage adjustment was observed.

Table IV. Rates of patient satisfaction (excellent plus good) at weeks 1 and 3 according to type of arthritis (N = 771).*

Type of Arthritis	Satisfaction (excellent plus good)
Osteoarthritis (%)	
Week 1	343/671 (51.1)
Week 3	414/542 (76.4)
Rheumatoid arthritis (%)	
Week 1	32/74 (43.2)
Week 3	43/58 (74.1)

*Patient numbers vary because patients were withdrawn throughout the study.

Table V. Rates of patient satisfaction (excellent plus good) at weeks 1 and 3 in patients who did or did not receive the brochure "Managing Your Arthritis."

	Satisfaction (excellent plus good)
Received brochure (%)	
Week 1	202/414 (48.8)
Week 3	251/329 (76.3)
Did not receive brochure (%)	
Week 1	172/327 (52.6)
Week 3	204/268 (76.1)

*Patient numbers vary because patients were withdrawn throughout the study.

This patient sample was representative of the clinical population seen by Canadian general practitioners in the field of chronic arthritis. The respective proportions of osteoarthritis and rheumatoid arthritis and their duration were as expected. Although it is commonly thought that the provision of written instructions to patients has an impact on patient compliance, there have been few data to document this effect. This study demonstrated that physician assessment of patient satisfaction did not differ significantly between patients who did receive the brochure and those who did not.

The frequency of adverse effects was consistent with other studies of salsalate.[17] A total of 234 patients (30.4%) discontinued therapy because of side effects that were judged by physicians as possibly or probably related to therapy. The most frequently reported reasons for discontinuation were GI disorders (13.2%) and tinnitus (6.7%). Although 78 patients expe-

rienced tinnitus, only 52 (6.7%) discontinued therapy for this reason.

CONCLUSIONS

This short-term study demonstrated that patient satisfaction with salsalate increased with length of therapy. The study also revealed that physicians are not likely to use the occurrence of tinnitus as a tool for establishing optimal salsalate dose. In addition, tinnitus was not a major reason for discontinuation of therapy nor was it a major impediment to patient satisfaction. Distribution of printed patient educational materials did not appear to increase patient satisfaction with therapy.

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