A case for rimantadine to be marketed in Canada for prophylaxis of influenza A virus infection

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F Marra, CA Marra, HG Stiver. A case for rimantadine to be marketed in Canada for prophylaxis of influenza A virus infection. Can Respir J 2003;10(7):381-388.

PURPOSE: To evaluate the efficacy and safety of amantadine and rimantadine, the first generation antivirals, for the prophylaxis of influenza virus.
DATA SOURCES: A systematic search of the English language literature using MEDLINE, EMBASE, Current Contents and the Cochrane database from 1966 to April 2002, as well as a manual search of references from retrieved articles, were performed.
STUDY SELECTION: Prospective, randomized, controlled clinical trials evaluating amantadine and rimantadine for prophylaxis of naturally occurring influenza A illness were considered. The control arm used either a placebo or an antiviral agent.
DATA EXTRACTION: Each trial was assessed by two authors to determine the adequacy of randomization and description of withdrawals. Efficacy data were extracted according to a predefined protocol. Discrepancies in data extraction among the investigators were solved by consensus. Nine prophylaxis studies of amantadine and rimantadine met the criteria for this systematic review.
DATA SYNTHESIS: Seven amantadine versus placebo trials (n=1797), three rimantadine versus placebo trials (n=688) and two amantadine versus rimantadine studies (n=455) were included for the meta-analysis on the prevention of influenza A illness. The summary of results for the relative odds of illness indicated a 64% reduction in the amantadine group compared with placebo (OR 0.36, 95% CI 0.23 to 0.55, P≤0.001), a 75% reduction in illness for the rimantadine group compared with placebo (OR 0.25, 95% CI 0.07 to 0.97, P=0.05) and no significant differences in the odds of illness for the amantadine versus rimantadine groups (OR 1.15, 95% CI 0.57 to 2.32, P=0.32). The summary of results examining adverse events showed significantly higher odds of central nervous system adverse reactions and premature withdrawal from the clinical trials in the amantadine-treated group than in the placebo-treated group. Compared with the placebo-treated group, the rimantadine-treated group did not have a significantly higher rate of withdrawal or central nervous system events. However, there was a significant increase in the odds of gastrointestinal adverse events for those treated with rimantadine compared with those treated with placebo (OR 3.34, 95% CI 1.17 to 9.55, P=0.03). In the comparative trials of amantadine to rimantadine, rimantadine was associated with an 82% reduction in the odds of central nervous system events (OR 0.18, 95% CI 0.03 to 1.00, P=0.05) and a 60% reduction in the odds of discontinuing treatment (OR 0.40, 95% CI 0.20 to 0.79, P=0.009).
CONCLUSION: This meta-analysis demonstrates that amantadine and rimantadine are superior to placebo in the prevention of influenza A illness. Both antiviral agents have an increased number of adverse events compared with placebo; however, the use of amantadine is associated with significantly higher numbers of central nervous system events and treatment withdrawals compared with rimantadine. Thus, rimantadine should be the preferred agent in this class for the prevention of influenza A virus infection and should be made available in Canada.

Key Words: *Amantadine; Influenza; Prophylaxis; Rimantadine*

Un argument en faveur de la commercialisation de la rimantadine au Canada pour la prophylaxie de l'infection au virus d'influenza A

OBJECTIF : Évaluer l'efficacité et l'innocuité de l'amantadine et de la rimantadine, des antiviraux de première génération, pour la prophylaxie du virus de l'influenza.
SOURCES DE DONNÉES : Une recherche systématique de la documentation scientifique anglophone au moyen des bases de données MEDLINE, EMBASE, Current Contents et Cochrane entre 1966 et avril 2002, de même qu'une recherche manuelle des références tirées des articles extraits, ont été effectuées.
SÉLECTION DES ÉTUDES : On a étudié des essais cliniques prospectifs aléatoires et contrôlés évaluant l'amantadine et la rimantadine pour la prophylaxie de l'infection naturelle au virus de l'influenza A. Les sujets témoins prenaient soit un placebo, soit un antiviral.
EXTRACTION DES DONNÉES : Chaque essai a été évalué par deux auteurs afin de déterminer la justesse de l'aléation et la description des désistements. Les données d'efficacité ont été extraites d'après un protocole prédéfini. Les écarts dans l'extraction des données entre les chercheurs ont été résolus par consensus. Neuf études prophylactiques de l'amantadine et de la rimantadine respectaient les critères de cette étude systématique.
SYNTHÈSE DES DONNÉES : Sept essais sur l'amantadine par rapport à un placebo (n=1 797), trois essais sur la rimantadine par rapport à un placebo (n=688) et deux essais sur l'amantadine par rapport à la rimantadine (n=455) ont été inclus dans la méta-analyse sur la prévention de l'influenza A. Le sommaire des résultats du risque relatif de la maladie indiquait une réduction de 64 % au sein du groupe traité à l'amantadine par rapport à celui prenant un placebo (RR 0,36, 95 % IC 0,23 à 0,55, P≤0,001), une réduction de 75 % de la maladie au sein du groupe traité à la rimantadine par rapport à celui prenant un placebo (RR 0,25 95 % IC

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0,07 à 0,97, P=0,05), et aucune différence au sein du groupe traité à l'amantadine par rapport à celui traité à la rimantadine (RR 1,15, 95 % IC 0,57 à 2,32, P=0,32). Le sommaire des résultats d'événements indésirables a révélé un risque considérablement plus élevé de réactions indésirables du système nerveux central et de désistements prématurés des essais cliniques au sein du groupe traité à l'amantadine que dans le groupe prenant un placebo. Comparativement au groupe prenant un placebo, le groupe traité à la rimantadine ne présentait pas un risque considérablement plus élevé de désistements ou de réactions du système nerveux central. Cependant, on remarquait une augmentation importante du risque de réactions gastro-intestinales chez les personnes traitées à la rimantadine par rapport à celles prenant un placebo (RR 3,34, 95 % IC 1,17 à 9,55, P=0,03). Dans le cadre des essais comparatifs de l'amantadine par rapport à la rimantadine, la rimantadine s'associait à une réduction de 82 % du risque de réactions du système nerveux central (RR 0,18, 95 % IC 0,03 à 1,00, P=0,05) et une réduction de 60 % du risque de désistements du traitement (RR 0,40, 95 % IC 0,20 à 0,79, P=0,009).

CONCLUSION : La présente méta-analyse démontre que l'amantadine et la rimantadine sont supérieures au placebo dans la prévention de l'influenza A. Ces deux antiviraux provoquent plus d'événements indésirables que le placebo, mais l'usage de l'amantadine s'associe à un nombre considérablement plus élevé de réactions du système nerveux central et de désistements du traitement que la rimantadine. Ainsi, la rimantadine devrait être l'agent favorisé au sein de cette classe de médicaments pour prévenir l'infection au virus de l'influenza A, et elle devrait être homologuée au Canada.

Epidemics of influenza occur during the winter months nearly every year and are responsible for approximately five million clinical infections, 50,000 hospitalizations and 5000 deaths per year in Canada. Economic losses due to this disease are in the range of $1.5 million per year (1,2). Influenza viruses can also cause global epidemics of disease, known as pandemics, during which rates of morbidity and mortality from influenza-related complications can increase dramatically (3-6). Influenza viruses cause disease in all age groups; rates of infection are highest among children, but rates of serious morbidity and mortality are highest among persons aged 65 years and older, and persons of any age who have underlying medical conditions that place them at a high risk for complications from influenza (7-9).

Efforts to prevent influenza deal primarily with immunoprophylaxis with inactivated vaccine and secondarily with chemoprophylaxis with influenza-specific antiviral agents. For nearly 50 years, the inactivated influenza vaccine has served as a cornerstone on which prevention programs are based. Annual vaccination is recommended for elderly persons and those with chronic medical conditions, and has been shown to significantly reduce the risk of severe illness, hospitalization and death in these populations (10). While from a societal perspective, the clinical, public health and economic benefits of influenza vaccination cannot be overstated, vaccine efficacy in any given year and for any given recipient may be variable (11). This variability depends on a complex interaction of: vaccine-related factors, including vaccine preparation, dose and degree of antigenic relatedness to circulating strains; virological and epidemiological factors, including the interval between vaccination and exposure, as well as the virulence and degree of transmissibility of the epidemic strains; and host factors such as age, underlying health status and prior antigenic experience. Under the ideal circumstance, in which there is a close match between the vaccine and epidemic strains, vaccine efficacy is typically in the range of 70% to 90% for healthy adults (2), with substantially lower estimates (30% to 50%) for frail elderly recipients such as nursing home residents (10). The variability in protective efficacy, combined with continued difficulties in raising vaccination coverage in certain high risk groups, translates to gaps in immunity that must be filled by other means.

The first generation of antiviral agents include amantadine hydrochloride and rimantadine hydrochloride (12). Amantadine and rimantadine are chemically related antiviral drugs with specific activity against influenza A viruses but not influenza B viruses (13). While amantadine has been available in North America, Europe, Asia and Australia since 1976, rimantadine was only approved in 1993 in the United States, Europe and Japan, and is not available in Canada, Australia or parts of Asia. There have been numerous clinical trials evaluating amantadine and rimantadine for prophylaxis of influenza A infection. However, they have usually been compared with placebo; only two trials have conducted a head-to-head comparison of the two antiviral agents. The purpose of this article is to pool the results of those studies to evaluate the efficacy and safety of amantadine and rimantadine for the prophylaxis of influenza virus.

SYSTEMATIC REVIEW – METHODS

Data sources

The literature for the period of January 1966 to April 2002 was searched using MEDLINE, EMBASE, Current Contents and the Cochrane database for articles and reviews pertaining to the prevention of influenza. The search terms used for this purpose were influenza, antivirals, amantadine and rimantadine. Further articles were identified from a manual search of the reference lists of articles and review papers.

Study selection

All randomized, double-blind, placebo-controlled, English language trials of amantadine or rimantadine for the prevention of influenza in adults (older than 16 years) were eligible for inclusion in the review. The control arm may have used placebo or an antiviral agent (amantadine or rimantadine). Only studies assessing protection from naturally occurring influenza A and those evaluating laboratory-confirmed influenza cases were considered for this review. Articles or data published in more than one citation, data published only in abstract form, unpublished data and data generated from clinical influenza-like illness only (ie, did not look at laboratory-confirmed cases), were excluded.

Data extraction

Each trial was read independently by two authors to assess the adequacy of randomization and description of withdrawals. Assessment of methodological quality was not performed within eligible trials. Data extracted included clinical trial design, number of patients randomized, number of patients used for analysis of results, age, sex, race, criteria for eligibility, type of antiviral, regimen of study drugs, length of follow-up, number and severity of laboratory-confirmed influenza cases, presence of side effects

and number of withdrawals due to adverse effects. Attempts were made to acquire additional information from investigators as required. Discrepancies of data extraction were resolved by group consensus through review of the published trial.

Statistical methods and sensitivity analysis

Trials were categorized either as studies of clinical outcomes of amantadine or rimantadine compared with placebo, or of amantadine compared with rimantadine for adverse events. Odds ratios (ORs) with 95% CIs and the summary ORs were calculated using the Dersimonian and Laird random effects model (14). A statistically significant result was assumed when the 95% CI of the OR of each trial did not include 1. Heterogeneity was assessed using the following methods, because the power of any one is low: a visual inspection of the graphical display of the trials' 95% CIs, ORs and summary ORs; the Cochran Q χ^2 test with a P value cut-off greater than 0.10 (15,16); and Galbraith plots (17). Where heterogeneity was detected, accepted methods for exploration of statistical heterogeneity using clinical parameters were used (18). Publication bias was investigated through visual inspection of funnel plots in which ORs were plotted against study sample size (15).

Robustness of the analysis was further evaluated using a technique based on the 'file drawer' problem (19). This technique is based on the premise that published journals are filled with only 5% of studies whereas a further 95% reside in 'file drawers' due to the lack of statistical significance of their results. Therefore, the number of unretrieved studies averaging null results required to bring the new overall P value to the brink of significance (P=0.05) was calculated for each end point. Robustness is typically set at 5k+10 studies, where k is equal to the number of originally identified studies.

RESULTS

Study selection and characteristics

We identified 20 randomized, prospective clinical trials that have evaluated the efficacy of amantadine and rimantadine for prophylaxis against naturally occurring influenza A infection (20-39). Out of the 20 studies, 12 were excluded (one crossover trial, one non-English language trial, four trials not placebo controlled, one trial in which children and adults were participants and five trials that evaluated clinical efficacy only, rather than a clinical and laboratory end point) (28-39). Of the remaining eight studies, five evaluated amantadine versus placebo (20-24), one evaluated rimantadine and placebo (25), and two evaluated amantadine, rimantadine and placebo (Table 1) (26,27). In addition, Table 2 shows the breakdown of adverse reactions seen in the prophylactic studies.

Amantadine versus placebo

The summary of results in 1797 patients from all seven studies reporting the illness end point indicated a 64% reduction in the odds of illness in the amantadine-treated group (OR 0.36,

TABLE 1
Randomized, double-blind, placebo-controlled studies included for prevention of natural influenza A virus

Agents	Study and year (reference)	Total number of patients*	Number of patients analysed†	Population	Age in years (range)	Regimen	Duration (weeks)	Laboratory-confirmed influenza ratio (%)	Efficacy§ (95% CI)
Amantadine and placebo	Oker-Blom et al, 1970 (20)	391	293	University students	22 (NA)	Amantadine 100 mg twice daily	6	16/141 (11)	59 (31 to 76)
						Placebo		41/152 (27)	
	Monto et al, 1979 (21)	286	275	University students	NA (18 to 24)	Amantadine 100 mg twice daily	7	8/136 (6)	70 (37 to 86)
						Placebo		28/139 (20)	
	Kantor et al, 1980 (22)	139	110	Military paramedics	22 (NA)	Amantadine 100 mg twice daily	2	9/59 (15)	17 (–95 to 64)
						Placebo		9/51 (18)	
	Pettersson et al, 1980 (23)	192	192	Military recruits	21 (NA)	Amantadine 100 mg twice daily	3,5‡	32/95 (34)	44 (23 to 60)
						Placebo		59/97 (61)	
	Reuman et al, 1989 (24)	476	476	Healthy adults	NA (18 to 55)	Amantadine 100 mg daily	6	3/317 (0.9)	70 (–72 to 95)
						Amantadine 200 mg daily			
						Placebo		5/159 (3)	
Rimantadine and placebo	Brady et al, 1990 (25)	228	222	Healthy adults	NA (18 to 55)	Rimantadine 100 mg daily	6	1/112 (0.9)	85 (–22 to 98)
						Placebo		7/110 (6)	
Amantadine, rimantadine and placebo	Quarles et al, 1981 (26)	444	308	University students	NA (18 to 24)	Amantadine 100 mg twice daily	6	15/107 (14)	30 (–30 to 62)
						Rimantadine 100 mg twice daily		15/102 (15)	25 (–38 to 59)
						Placebo		20/99 (20)	
	Dolin et al, 1982 (27)	450	378	Healthy adults	26 (18 to 45)	Amantadine 100 mg twice daily	6	2/113 (2)	90 (65 to 97)
						Rimantadine 100 mg twice daily		4/133 (3)	85 (58 to 95)
						Placebo		27/132 (20)	

**Total number of patients randomized into the study; †Number of patients evaluated for efficacy; ‡The study had two groups: group 1 received drugs for three weeks and group 2 received drugs for five weeks; §Efficacy relative risk reduction = (rate in placebo recipients – rate in amantadine recipients x 100%) / rate in placebo recipients. NA Not available*

95% CI 0.23 to 0.55, P<0.001) (Table 3, Figure 1). The Cochran Q test for heterogeneity of treatment effect of these studies was not significant (P=0.32). Visual inspection of the corresponding funnel plot revealed the possibility of publication bias for trials favouring amantadine.

For the comparison of adverse events between amantadine and placebo in 3430 patients, there was no significant increase in the odds of any adverse event (OR 1.56, 95% CI 0.87 to 2.81, P=0.14) (Table 3). For central nervous system (CNS) adverse events assessed in 4327 patients, there wer significantly higher odds of these events in the amantadine group than in the placebo group (OR 2.52, 95% CI 1.34 to 4.72, P=0.004). In 2191 patients assessed for premature withdrawal of treatment, there were significantly higher odds of discontinuing therapy in the amantadine group than in the placebo group (OR 2.68, 95% CI 1.66 to 4.34, P<0.001).

TABLE 2
Proportions of subjects with adverse effects to study drugs for the prevention of influenza infection

Study (reference)	Amantadine ratio (n)	%	Rimantadine ratio (n)	%	Placebo ratio (n)	%
Central nervous system*						
Oker-Blom et al (20)	22/141	16	–	–	6/152	4
Monto et al (21)	92/144	64	–	–	72/142	51
Kantor et al (22)	9/59	15	–	–	0/51	0
Reuman et al (24)	70/317	22	–	–	25/159	16
Brady et al (25)	–	–	5/114	4	3/114	3
Dolin et al (27)	19/145	13	9/147	6	6/148	4
Gastrointestinal						
Reuman et al (24)	29/317	9	–	–	12/159	8
Brady et al (25)	–	–	6/114	5	3/114	3
Other						
Monto et al (21)†	2/144	1	–	–	1/142	0.7
Kantor et al (22)‡	1/59	2	–	–	0/51	0
Reuman et al (24)§	2/317	0.6	–	–	1/159	0.6
All adverse reactions						
Monto et al (21)	2/144	1	–	–	1/142	0.7
Pettersson et al (23)	20/246	8	–	–	34/255	13
Reuman et al (24)	118/317	37	–	–	49/159	31
Brady et al (25)	–	–	10/114	9	5/114	4
Quarles et al (26)	18/107	17	24/102	24	12/99	12
Withdrawals						
Oker-Blom et al (20)	2/141	1	–	–	0/152	0
Monto et al (21)	12/144	8	–	–	3/142	2
Pettersson et al (23)	18/117	15	–	–	7/108	6
Reuman et al (24)	2/317	0.6	–	–	1/159	0.6
Quarles et al (26)	6/107	6	2/102	2	4/99	4
Dolin et al (27)	23/145	16	10/147	7	7/148	2

**Includes insomnia, headache, difficulty in concentration and lightheadedness; †Rash; ‡Impotence; §Cardiovascular*

Rimantadine versus placebo

The summary of results in 688 patients from all three studies reporting the illness end point indicated a 75% reduction in the odds of illness in the rimantadine-treated group (OR 0.25, 95% CI 0.07 to 0.97, P=0.05) (Table 4, Figure 2). The Cochran Q test for heterogeneity of treatment effect of these studies was not significant (P=0.48). Visual inspection of the corresponding funnel plot revealed no evidence of publication bias.

In contrast to amantadine, there was a significant increase in the odds of any adverse event when rimantadine was compared with placebo (OR 1.96, 95% CI 1.19 to 3.22, P=0.008). For gastrointestinal (GI) adverse events, the odds of occurrence for those treated with rimantadine were higher than for those treated with placebo (OR 3.34, 95% CI 1.17 to 9.55, P=0.025). The ORs for CNS adverse events and treatment withdrawals were not significantly higher for those taking rimantadine than for those taking placebo (Table 5).

Amantadine versus rimantadine

In the 455 patients involved in the two comparative trials of amantadine versus rimantadine, there were no significant differences in the odds of illness or any adverse event (Table 5). However, for CNS adverse events, there was a 82% reduction in the odds of occurrence with rimantadine (OR 0.18, 95% CI 0.03 to 1.00, P=0.05), and for treatment withdrawal, there was a 60% reduction in the odds of discontinuing treatment associated with rimantadine (OR 0.40, 95% CI 0.20 to 0.79, P=0.009) (Table 5).

Heterogeneity and sensitivity analyses

Visual inspection of the vertical lines drawn through the summary OR for each assessed end point indicated that the vertical line intersected most of the horizontal lines (representing the 95% CI for each individual trial). The Galbraith plots for

TABLE 3
Odds ratios (95% CIs) for amantadine versus placebo clinical trials

Study (reference)	Outcome: Laboratory-confirmed influenza	Adverse events: Any	Withdrawal	Central nervous system	Gastrointestinal
Oker-Blom et al (20)	0.35 (0.13 to 0.94)	NA	9.8 (0.16 to 617.53)	4.37 (0.76 to 25.04)	NA
Monto et al (21)	0.25 (0.08 to 0.78)	1.99 (0.13 to 29.36)	3.97 (1.141 to 13.80)	1.72 (0.36 to 8.15)	NA
Kantor et al (22)	0.84 (0.24 to 2.96)	NA	NA	37.74 (0.53 to 2671.0)	NA
Pettersson et al (23)	0.33 (0.13 to 0.86)	0.58 (0.15 to 2.18)	2.74 (1.14 to 6.60)	NA	NA
Reuman et al (24)	0.30 (0.06 to 1.49)	1.33 (0.38 to 4.72)	0.90 (0.10 to 8.12)	1.51 (0.32 to 7.24)	1.23 (0.35 to 4.40)
Quarles et al (26)	0.65 (0.23 to 1.86)	1.52 (0.36 to 6.36)	1.43 (0.40 to 5.05)	NA	NA
Dolin et al (27)	0.078 (0.016 to 0.380)	NA	3.705 (1.555 to 8.830)	3.470 (0.601 to 20.052)	NA
Summary	**0.36 (0.23 to 0.55)**	**1.56 (0.87 to 2.81)**	**2.68 (1.66 to 4.34)**	**2.52 (1.34 to 4.72)**	**2.18 (0.96 to 4.94)**
Test for heterogeneity*	**0.32**	**0.30**	**0.70**	**0.20**	**0.28**

**Cochrane's Q test for heterogeneity. NA Not available*

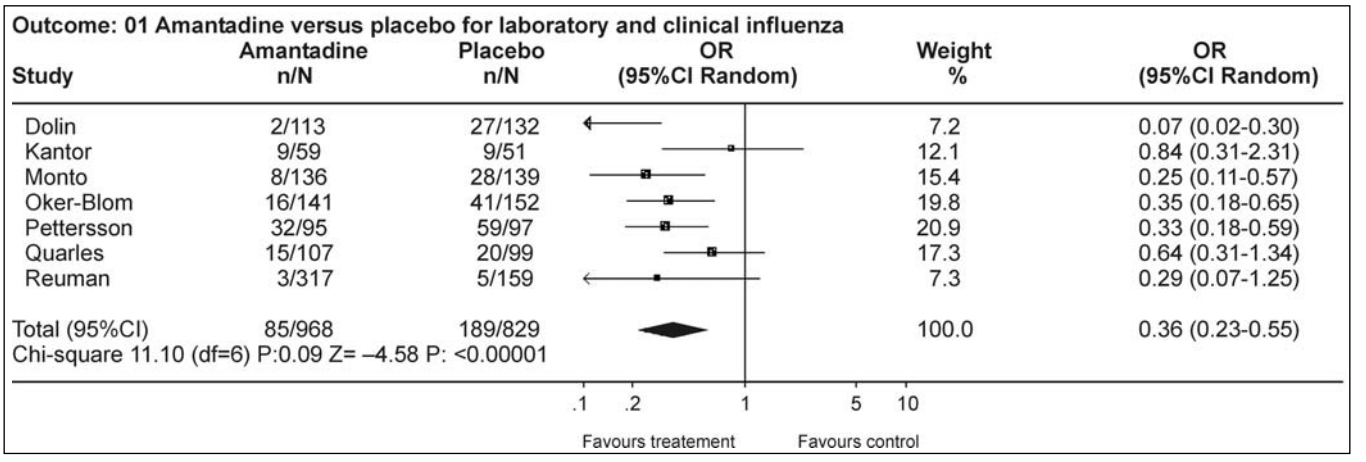

Figure 1) *Results of amantadine versus placebo for the prevention of laboratory-confirmed influenza. Data taken from references 20 to 24, 26 and 27. OR Odds ratio*

TABLE 4
Odds ratios (95% CIs) for rimantadine versus placebo clinical trials

Study (reference)	Outcome: Laboratory-confirmed influenza	Adverse events: Any	Withdrawal	Central nervous system	Gastrointestinal
Brady et al (25)	0.13 (0.007 to 2.35)	2.10 (0.69 to 6.34)	NA	1.70 (0.39 to 7.28)	2.10 (0.50 to 8.48)
Quarles et al (26)	0.68 (0.09 to 5.47)	2.23 (1.04 to 4.76)	0.48 (0.09 to 2.66)	NA	NA
Dolin et al (27)	0.12 (0.01 to 1.12)	NA	1.47 (0.54 to 3.97)	1.54 (0.54 to 4.45)	NA
Summary	**0.25 (0.07 to 0.97)**	**1.96 (1.19 to 3.22)**	**1.10 (0.48 to 2.51)**	**1.255 (0.67 to 2.36)**	**3.34 (1.17 to 9.55)**
Test for heterogeneity[2]	**0.48**	**0.85**	**0.54**	**0.72**	**0.32**

**Cochrane's Q test for heterogeneity. NA Not available*

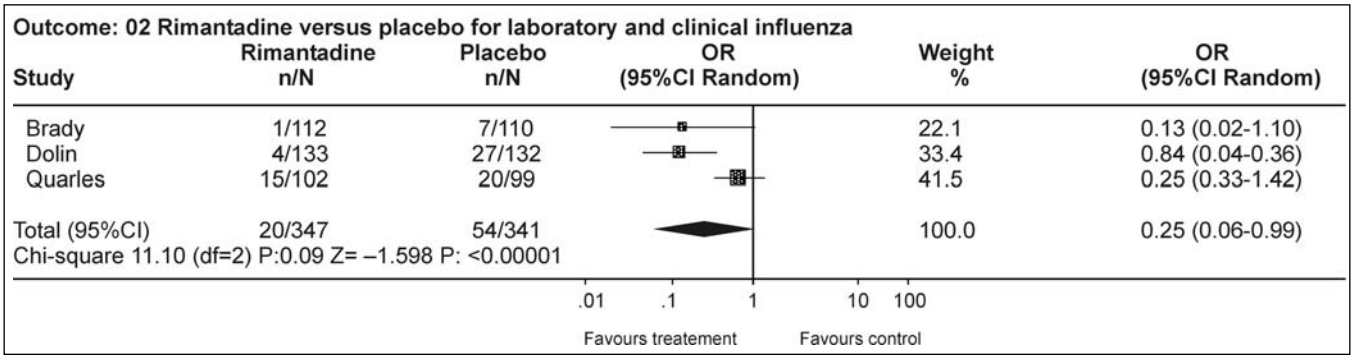

Figure 2) *Results of rimantadine versus placebo for the prevention of laboratory-confirmed influenza. Data taken from references 25 to 27. OR Odds ratio*

TABLE 5
Odds ratios (95% CIs) for amantadine versus rimantadine clinical trials

Study (reference)	Outcome: Laboratory-confirmed influenza	Adverse events: Any	Withdrawal	Central nervous system	Gastrointestinal
Quarles et al (26)	1.06 (0.49 to 2.29)	0.66 (0.06 to 7.82)	2.97 (0.59 to 15.08)	NA	NA
Dolin et al (27)	1.72 (0.31 to 9.58)	NA	2.58 (1.18 to 5.64)	2.31 (0.20 to 26.25)	NA
Summary	**1.15 (0.57 to 2.32)**	**1.60 (0.28 to 9.27)**	**2.49 (1.26 to 4.93)**	**5.54 (0.99 to 31.00)**	**NA**
Test for heterogeneity[2]	**0.61**	**0.32**	**0.77**	**0.32**	**NA**

**Cochrane's Q test for heterogeneity. NA Not available*

the prevention of influenza A were analyzed for evidence of statistical heterogeneity (18). For the prevention studies evaluating amantadine and placebo, none of the trials were demonstrated to be statistically heterogeneous. For comparisons between rimantadine and placebo, the trial by Quarles et al (26) fell outside the region of homogeneity. For comparison between amantadine and rimantadine for prophylaxis of influenza A infection, none of the trials fell outside this region and were thought to be statistically heterogeneous.

Techniques used to solve the 'file drawer' problem revealed that 58 studies averaging null results must be overlooked before one would conclude that the overall results were due to sampling bias in the studies summarized by the reviewer. The limit for robustness for this review was defined as 5k+10 trials, in which k equals the number of trials included in the analysis. By this method, the threshold value for all end points was 55 trials, respectively; therefore, the present results are robust and cannot be influenced by the appearance of several trials with neutral results.

DISCUSSION

The evidence from individual clinical trials shows that the protective efficacy of amantadine or rimantadine for prophylaxis of influenza A infection ranges from 59% to 100%, which is comparable to that obtained with inactivated influenza A virus vaccines. The findings of this meta-analysis indicate that amantadine and rimantadine are superior to placebo in preventing influenza A illness, but no difference was observed between the two active treatments. It should be noted that we included three studies in this meta-analysis that had significant faults that may have skewed the results (22,23,26). Kantor et al (22) reported that over 50% of the participants in the placebo group had hemagglutin inhibition titres of 1:20 or more, together with less than optimal compliance with study medications. It has been shown that titres as low as 1:16 can offer some protection against wild type influenza (40), and therefore, insufficient numbers of the population studied may have been immunologically vulnerable enough to show a large difference between amantadine and placebo. In the studies conducted by Pettersson et al (23) and Quarles et al (26), low rates of illness were observed in the placebo group, as well as in the amantadine or rimantadine groups, suggesting that many observed antibody rises resulted from exposure just before the study began. This may have resulted in the low rates of protection observed with amantadine and rimantadine.

The clinical trials evaluated for this systematic review show that orally administered amantadine and rimantadine are generally well tolerated, with no serious renal, hepatic or hematological toxicities. The most common side effects are GI and CNS effects, including nervousness, anxiety, difficulty concentrating and lightheadedness. Side effects with both drugs are usually mild, can diminish or disappear after the first week – despite continued drug ingestion – and cease soon after discontinuing the drug.

Our meta-analysis showed that the incidence of CNS side effects and treatment-related withdrawals is higher among persons taking amantadine than among those taking rimantadine or placebo. The CNS side effects of amantadine are thought to be related to the differences in the pharmacokinetics of the two antiviral agents and is believed to be dose-dependent (41). Doses of 300 mg/day are associated with decreased psychomotor performance such as diminished attention spans and problem-solving abilities, marked behavioural changes, delirium, hallucinations, agitation and seizures (42). These more severe side effects are associated with steady state trough plasma concentrations of 0.45 μg/mL or peak concentrations of more than 1.0 μg/mL, and have been observed most often among persons who have renal insufficiency, seizure disorders or certain psychiatric disorders, and also among elderly persons who have been taking amantadine as prophylaxis at a dose of 200 mg/day (43). Clinical observations and studies have indicated that lowering the dose of amantadine among these persons reduces the incidence and severity of such side effects. Thus, careful observation is advised when amantadine is administered concurrently with drugs that affect the CNS; concomitant administration of antihistamines or anticholinergic drugs may increase the incidence of adverse CNS reactions.

Evidence from individual clinical trials suggests that GI side effects occur in approximately 1% to 3% of persons taking either amantadine or rimantadine, compared with 1% of persons receiving the placebo, and that the incidence of these effects with rimantadine is approximately the same as with amantadine. However, in our meta-analysis, rimantadine was associated with a higher incidence of GI adverse events than amantadine or placebo. In summary, based on the results of this meta-analysis on adverse events and treatment-related withdrawals, rimantadine is a better choice than amantadine for the prevention and treatment of influenza infection.

A similar meta-analysis was conducted by members of the Cochrane Collaboration in 2002 (44). Our study differs in that we only included studies that evaluated laboratory-confirmed influenza, whereas the Cochrane Collaboration also evaluated studies with clinically-confirmed influenza. This is because we feel that discrepant and inaccurate results can be derived from including purely clinical illness as an end point for the meta-analysis in influenza preventative studies. For example, in one of the trials, there was a large discrepancy between the efficacy of amantadine for clinical respiratory illness versus laboratory-confirmed influenza cases (24). This occurred because of concomitant adenovirus illness in the study population, which could not be distinguished clinically from influenza. Recognizing this problem, we based the meta-analysis only on laboratory-confirmed influenza rates.

In a meta-analysis, it is important to investigate the presence and sources of statistical heterogeneity (18). We used a random effects model that accounted for heterogeneity among the ORs of pooled studies. In addition, we used Cochran's Q test for the presence of statistical heterogeneity and were unable to identify its presence via this method. However, statistical tests for heterogeneity have low power, and thus, heterogeneity cannot be ruled out solely through their use. Therefore, other methods should also be used (19). By visual inspection of the graphical representations of the trials and Galbraith plots, heterogeneity in our results was revealed for both amantadine and rimantadine when infection was used as the end point. Through the use of the Galbraith plots, we attempted to qualify possible sources of heterogeneity within these trials. Although potential differences were located and discussed in the results

section, the small number of trials identified makes it impossible to determine with any certainty whether these sources of heterogeneity were real or due to chance.

The influence of publication bias must be considered in any meta-analysis (45). We attempted to detect this source of bias through the construction of funnel plots. This plot allowed us to assess, through visual inspection, whether most of the articles that were included in our analyses reported positive results. Fortunately, it appeared that there were an approximately equal number of both positive and negative trials, making publication bias less likely. In addition, we used calculations for the 'file drawer' problem to determine the number of papers averaging null results required to have been overlooked to bring our results to the brink of significance; the numbers generated by these calculations identified that our analysis was robust. Because we limited our inclusion criteria to articles published in English language journals, we excluded one article. However, there is little reason to believe that the results of this study would have been so divergent from the published English language literature as to change the results of this analysis. Finally, because covert duplicate publication is a direct threat to meta-analyses (46), we examined all trials for evidence of this practice. Fortunately, we were unable to locate any trials that contained information that had obviously been previously published.

Several important limitations of this meta-analysis should be recognized. As in any meta-analysis of previously published results, this analysis relied on information from trials with differences in study design, end points, enrollment characteristics and treatment regimens. Consequently, although every effort was made to standardize the extraction of relevant information to outcomes, available data and definitions of outcomes varied among studies. We also did not account for differences in dose regimens among trials and combined results based solely on the type of treatment used. A limitation of this approach is that possible dose-related differences in effect are not considered. We could have performed a subgroup analysis by dose; however, the sample sizes would have been too small to yield meaningful results.

An additional limitation of this meta-analysis is that only studies pertaining to seasonal prophylaxis of influenza in the healthy adult population have been evaluated; the results of this meta-analysis can, therefore, only be extrapolated to that population. Although amantadine and rimantadine are used frequently for the management of outbreak control in nursing homes and, to a lesser extent, postexposure prophylaxis in families, our literature search did not reveal any controlled trials evaluating their efficacy or safety in these two situations. However, studies comparing the safety of these two antiviral agents in elderly persons show that a larger percentage of patients develop CNS side effects from amantadine (19%) than from rimantadine (2%), and that more patients discontinue treatment with amantadine (17%) than with rimantadine (2%) (47,48). Our meta-analysis showed that CNS adverse events were more common with amantadine than with rimantadine in healthy adults. Thus, because the elderly are more prone to CNS adverse events, rimantadine is likely to be a safer agent.

CONCLUSION

The evidence from this systematic review shows that both amantadine and rimantadine are superior to placebo in the prevention of influenza A illness. Although both antiviral agents have more adverse events than placebo, the use of amantadine is associated with more CNS adverse events and treatment withdrawals. Therefore, rimantadine is a better drug for the prevention of influenza A infection and should be available in Canada.

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