

Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis

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Abstract

Background: The use of antidepressant medications and the resulting costs have increased dramatically in recent years, partly because of the introduction of selective serotonin reuptake inhibitors (SSRIs). An assessment of the clinical and economic aspects of SSRIs compared with the older tricyclic antidepressants (TCAs) was initiated to generate information for purchasers of these drugs as well as clinicians. One component of this study was an examination of the adverse effects associated with the use of these drugs.

Methods: Searches of bibliographic databases (for January 1980 through May 1996) and manual scanning of both peer-reviewed publications and other documents were used to identify double-blind, randomized controlled trials involving at least one SSRI and one TCA. For the study of adverse effects, only trials that had at least 20 patients in each trial arm and that reported rates of adverse effects in both arms were retained. In total 84 trials reporting on 18 adverse effects were available. Meta-analyses were undertaken to calculate pooled differences in rates of adverse effects. The question of whether the method of eliciting information from patients about adverse effects made a difference in the findings was also examined. Finally, differences in drop-out rates due to adverse effects were calculated.

Results: The crude rates of occurrence of adverse effects ranged from 4% (palpitations) to 26% (nausea) for SSRIs and from 4% (diarrhea) to 27% (dry mouth) for TCAs. The differences in the rates of adverse effects between the 2 types of drugs ranged from 14% more with SSRIs (for nausea) to 11% more with TCAs (for constipation). The results did not depend on the method of eliciting information from patients. There were no statistically significant differences between drug classes in terms of drop-outs due to adverse effects.

Interpretation: SSRIs and TCAs are both associated with adverse effects, although the key effects differ between the drug classes. Further explanation of the adverse effects and their relation to discontinuation of medication will require better studies involving prospective collection of quality-of-life data.

Résumé

Contexte : L'utilisation des antidépresseurs et les coûts qui en découlent ont augmenté de façon spectaculaire depuis quelques années, en partie à cause de l'avènement des inhibiteurs spécifiques du recaptage de la sérotonine (ISRS). On a entrepris une évaluation des aspects cliniques et économiques des ISRS par rapport à ceux d'antidépresseurs tricycliques (ATC) afin de produire de l'information pour les acheteurs de ces médicaments et les cliniciens. Un volet de l'étude a consisté à examiner les effets indésirables associés à l'utilisation de ces médicaments.

Méthode : On a effectué à la fois des recherches dans des bases de données biblio-



Evidence

Études

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graphiques (de janvier 1980 jusqu'à mai 1996) et une exploration manuelle parmi des publications critiquées par des pairs et d'autres documents pour trouver des études contrôlées randomisées à double insu portant sur au moins un ISRS et un ATC. Pour l'étude des effets indésirables, on n'a retenu que les études cliniques portant sur au moins 20 patients de chaque volet de l'étude et à la suite desquelles on a signalé des taux d'effets indésirables dans les deux volets. Au total, 84 études indiquant 18 effets indésirables étaient disponibles. On a entrepris des méta-analyses pour calculer les différences communes des taux d'effets indésirables. On a aussi cherché à déterminer si la façon d'obtenir des patients de l'information sur les effets indésirables a fait une différence dans les résultats. Enfin, on a calculé les différences des taux d'abandon à cause des effets indésirables.

Résultats : Les taux bruts d'occurrence d'effets indésirables ont varié de 4 % (palpitations) à 26 % (nausées) dans le cas des ISRS et de 4 % (diarrhée) à 27 % (bouche sèche) dans celui des ATC. Les différences des taux d'effets indésirables entre les deux types de médicaments ont varié de 14 % de plus avec les ISRS (nausées) à 11 % de plus avec les ATC (constipation). Les résultats ne dépendaient pas de la façon d'obtenir les renseignements des patients. Il n'y avait pas de différences significatives sur le plan statistique entre les catégories de médicaments en ce qui concerne les abandons à cause des effets indésirables.

Interprétation : On établit un lien entre les ISRS et les ATC et les effets indésirables, même si les principaux effets diffèrent entre les catégories de médicaments. Pour expliquer davantage les effets indésirables et leur lien avec l'abandon des médicaments, il faudra réaliser de meilleures études comportant la collecte prospective de données sur la qualité de vie.

Depression is a common disorder with significant health and cost implications. It has been estimated that up to 1 in 8 people in the United States may require treatment for depression during their lifetime.^{1,2} The Canadian National Population Health Survey of 1994/95 indicated that an estimated 6.9% or about 1.7 million Canadians 12 years of age or older had experienced symptoms of depression within the previous 2 months.

Pharmacotherapy and psychotherapy, individually or in combination, are the 2 most common treatments. Various drugs have been developed and used in treating depression. All of them have risks as well as benefits. Until recently, tricyclic antidepressants (TCAs) were the first-line class of antidepressants. They have been reported to cause anticholinergic side effects, including dry mouth, constipation, blurred vision, urinary retention and postural hypotension. Cardiac arrhythmias or palpitation may also occur. Selective serotonin reuptake inhibitors (SSRIs) are a new class of antidepressants that includes fluoxetine, fluvoxamine, paroxetine and sertraline. These drugs have been associated with nausea, diarrhea, insomnia, nervousness, agitation and anxiety.

A number of cost-effectiveness studies of these drug classes have been published recently.^{3,4} The cost of treating some of these adverse effects has been cited as a major contributor to the overall costs of drug therapy.⁵ How-

ever, cost-effectiveness studies have not considered treatment strategies for managing the adverse effects. Adverse effects leading to discontinuation of medication may, in fact, be associated with discomfort and loss of productivity and other indirect costs attributable to treatment failure.

In this paper we report on a meta-analysis of trials comparing TCAs with SSRIs, in which adverse effects data are reported.

Methods

Searching techniques

This paper is based on a larger study of clinical trials of antidepressant therapy.⁶ For that study, the following bibliographic databases were searched for the period January 1980 to May 1996: MEDLINE, EMBASE, PsycINFO, International Pharmaceutical Abstracts, Pascal, Health Planning and Administration (Health), Mental Health Abstracts, and Adis PharmacoEconomics and Outcomes News. In addition, studies identified through regular searches of *Current Contents: Clinical Medicine* and hand-scanning of journals received by the Canadian Coordinating Office of Health Technology Assessment library throughout the study period were also reviewed. Key words used for the searches included "serotonin uptake inhibitor(s)" or "SSRI(s)" or "antidepressant(s)" or "monoamine oxidase inhibitor(s)" or "anti-



depressive agents,” “tricyclic,” and the names of the various drugs. The main searches were then restricted to references to randomized controlled trials (RCTs), clinical trials or reviews. The references from all of the articles retrieved were also scanned, and further references were obtained from bibliographies provided by other researchers. Earlier publications on this subject, in particular the US Agency for Health Care Policy and Research clinical practice guidelines¹² and the UK National Health Service, Centre for Reviews and Dissemination bulletin,⁷ were used to identify additional references. More than 1100 articles were identified by this strategy. Of these, 104 were RCTs comparing SSRIs and TCAs.

Inclusion and exclusion criteria

This review was restricted to articles that reported on double-blind RCTs, of 4 to 12 weeks' duration, comparing an SSRI with a TCA for major depression (as defined by DSM-IV criteria⁸); 84 studies met these criteria (Appendix 1), and more than 50 different adverse effects were reported in these trials. The trials that were included in our study had at least 20 patients in each arm and reported the numbers of patients with adverse effects in both the SSRI and the TCA arms; only adverse effects for which there were data from at least 6 trials were studied. This reduced the number of adverse effects studied to 18: headache, tremor, urinary disturbances, hypotension, dry mouth, constipation, dizziness, sweating, blurred vision, palpitations, nausea, anorexia, diarrhea, insomnia, nervousness, fatigue, agitation and anxiety (Tables 1 and 2). Some well-established side effects, such as sexual dysfunction and weight loss, were not included in this analysis because of the lack of comparative evidence in the literature extracted. Rare events, such as suicide, were not examined for the same reason.

Estimation of occurrence of adverse effects

For each of the 18 adverse effects, the rates of occurrence in the SSRI and TCA arms in each trial were extracted or calculated from the data reported in the trial. From these, the difference in rates between the 2 arms was calculated for each trial. Finally, for each adverse effect, a “pooled” rate difference was obtained by a Bayesian hierarchical meta-analysis, which combined individual rate differences numerically, with weights that incorporated the uncertainty arising from the inherent variability of each trial (sampling) as well as the random variation between the trials. This analysis was done with Fast*Pro software.⁹ The analysis yielded a value for the pooled rate difference for each adverse effect, along with 95% confidence intervals.

Effects of method of eliciting information about adverse effects

A number of the 84 trials reported on the methods by which information on adverse effects was obtained from the patients. These methods included checklists, questions that indirectly addressed adverse effects, spontaneous reporting by the patient and the Dosage Record and Treatment Emergent Symptom Scale, with or without dosage record.¹⁰ In some cases the method was not explicitly stated. For 2 of the 18 adverse effects (nausea and dry mouth), the hypothesis that the method of eliciting information would influence reported occurrence rates and rate differences was tested. This was done by first subgrouping the trials according to the method of eliciting information and then, within each subgroup, calculating the pooled weighted rate difference between SSRIs and TCAs for each of the 2 adverse effects. As before, this pooling combined rate differences between the SSRI and TCA arms from each individual trial and weighted each rate difference according to the variability of each trial (sampling), as well as the random variation across settings.

Drop-outs due to adverse effects

Seventy of the 84 trials reported data on drop-outs due to adverse effects for both drugs. For each trial, the difference in rate of drop-outs due to adverse effects between the SSRI arm and the TCA arm was calculated. For this set of trials, these individual rate differences were again combined using meta-analysis to obtain an estimate of the pooled rate difference in drop-outs due to adverse effects between SSRIs and TCAs.

Results

Estimation of occurrence of adverse effects

Adverse effects are associated with the use of any anti-depressant. The crude rates of occurrence of each of the 18 adverse effects studied are shown in Table 1.

When the rate differences for individual trials were pooled, the 18 adverse effects fell into 4 categories: those for which there was no statistically significant difference between any 1 of the 4 SSRIs and the TCAs as a whole (headache, tremor, urinary disturbance and hypotension), those that occurred statistically significantly more often with TCAs than with at least one of the SSRIs (dry mouth, constipation, dizziness, sweating, blurred vision and palpitations), those that occurred statistically significantly more often with at least one of the SSRIs than with TCAs (nausea, anorexia, diarrhea, insomnia, nervousness and fatigue) and those for which there were no significant

rate differences between any individual SSRI and the group of TCAs (agitation and anxiety). However, for these 2 adverse effects, there was a statistically significant difference when the SSRI data were pooled.

Table 2 presents the results of these meta-analyses and shows the pooled weighted difference in rates by individual adverse effect.

When data for all of the SSRIs were pooled and compared with data for the TCAs, there were 7 adverse effects that occurred statistically significantly more often with SSRIs (nausea, anorexia, diarrhea, insomnia, nervousness, agitation and anxiety) and 5 that occurred statistically significantly more often with TCAs (dry mouth, constipation, dizziness, sweating and blurred vision).

Effects of method of eliciting information about adverse effects

For 2 of the 18 adverse effects (nausea and dry mouth), an analysis was done to determine if the methods used to obtain information from patients on the occurrence of adverse effects themselves had an effect on the reported rates. The difference in reported pooled rates of occurrence of nausea was 10% more with SSRIs than with TCAs when based on a checklist, 7% more when based

on spontaneous reports, 12% more when based on indirect questioning, 9% more when based on the Treatment Emergent Symptom Scale with or without dosage record and 15% more when information was obtained by unspecified methods. These rate differences were statistically significant for all methods of elicitation except the Treatment Emergent Symptom Scale. For dry mouth, the pooled rate of occurrence was 22% more with TCAs than with SSRIs when based on a checklist, 31% more when based on spontaneous reports, 25% more when based on indirect questioning, 32% more when based on the Treatment Emergent Symptom Scale with or without dosage record and 42% more when information was obtained by unspecified methods. All of these differences were statistically significant per se but were not statistically different from one another.

Drop-outs due to adverse effects

Seventy of the RCTs reported rates of drop-outs in each arm due to adverse effects. When the rates of discontinuation for patients receiving individual SSRIs or any SSRI were compared with the rates for secondary amines, tertiary amines, quaternary amines or any of the TCAs, there were no statistically significant differences. Among

Table 1: Crude rates* of occurrence of 18 adverse effects reported in 84 randomized controlled trials of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)

Adverse effect†	No. of trials	Type of drug; no of patients				Type of drug; crude rate,‡ %		Crude rate difference, %
		SSRIs		TCAs		SSRIs	TCAs	
		With adverse effect	Total	With adverse effect	Total			
Constipation	49	315	2789	614	2790	11	22	-11
Dizziness	37	311	2229	514	2214	14	23	-9
Hypotension	8	27	289	47	301	9	16	-6
Dry mouth	56	660	3008	810	2954	22	27	-5
Blurred vision	19	102	1072	141	1005	10	14	-5
Sweating	27	173	1653	225	1605	10	14	-4
Urinary disturbance	14	67	1165	98	1133	6	9	-3
Palpitations	11	38	1029	54	1068	4	5	-1
Fatigue	23	128	1318	143	1296	10	11	-1
Tremor	37	296	2000	285	1904	15	15	-0
Anorexia	11	95	1030	72	940	9	8	2
Nervousness	14	104	755	72	687	14	10	3
Agitation	11	76	613	44	543	12	8	4
Headache	32	297	1649	219	1598	18	14	4
Insomnia	32	232	1903	129	1829	12	7	5
Anxiety	17	113	825	62	841	14	7	6
Diarrhea	15	146	889	32	718	16	4	12
Nausea	56	750	2936	323	2868	26	11	14

*Crude rates and crude rate differences are biased estimates because variability within the sample and between the samples is not included. Crude rate differences were calculated from unrounded crude rates, but both crude rates and crude rate differences are presented here as whole numbers only. Therefore, some crude rate differences do not correspond exactly to the crude rates presented here (e.g., for hypotension).

†In order of crude rate difference.

‡Percentage of patients with the adverse effect.



patients receiving any SSRI, there were 11% fewer discontinuations than among patients receiving secondary amines, 3% fewer than among those receiving tertiary amines, 3% fewer than those receiving quaternary amines and 3% fewer than those receiving any TCA, but these differences were not statistically significant. However, a subset meta-analysis of trials restricted to adult outpatients indicated that there were 2% fewer drop-outs due to adverse effects with the SSRIs, a significant difference.⁶

Interpretation

All antidepressants cause adverse effects. In this study we found that SSRIs precipitate some adverse effects significantly more often than TCAs do (see Table 2): nausea, anorexia, diarrhea, insomnia, nervousness, anxiety and agitation. The analysis suggested that paroxetine may induce less nausea than the other SSRIs, but the evidence for this difference was weak.

However, there are other adverse effects that occur significantly less frequently with SSRIs than with TCAs. These are mainly anticholinergic symptoms such as dry

mouth, constipation, dizziness, sweating and blurred vision.

These adverse effects may have further clinical implications. Because the SSRI-associated adverse effects seem to be related to drug dose,¹¹ the occurrence of these effects may reflect a functional increase in central serotonin activity or serotonin sensitivity. This clearly has an excitatory role in pituitary–adrenal regulation. It is therefore physiologically possible that the worsening of hyperarousal symptoms may be associated with an increased capacity to take one's own life.¹² However, the debate concerning suicide continues. Unfortunately, there are insufficient data from the randomized trials reviewed to allow comparative analyses⁶ of rare adverse events, such as suicide. (The UK Centre for Health Economics summarized a thorough description of the uncertainties surrounding this debate in 1994.¹³)

Although there were no statistically significant differences between SSRIs as a group and TCAs as a group in the occurrence of 6 of the effects studied, some of the differences for these effects may have clinical significance and have in fact been debated over the past decade. In particular, postural hypotension, particularly in elderly pa-

Table 2: Pooled differences between SSRIs and TCAs in percentages of patients reporting adverse effects

Adverse effect	SSRI; pooled difference relative to TCAs, %				
	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	All SSRIs
Adverse effects for which there was no statistically significant difference between any 1 of the 4 SSRIs and all TCAs					
Headache	+2	+2	-2	+4	+2
Tremor	-2	+1	-2	+5	-1
Urinary disturbance	-2	-2	+1	-2	-1
Hypotension	-9	-17	+12	+2	-5
Adverse effects that occurred statistically significantly more often with TCAs than with at least one of the SSRIs					
Dry mouth	-32*	-22*	-21*	-30*	-29*
Constipation	-14*	-6	-4*	-10*	-11*
Dizziness	-13*	-6*	-8*	-7	-9*
Sweating	-3	-8*	-5	+1	-3*
Blurred vision	-5*	+1	-2	-4	-3*
Palpitations	-1	+3	-4*	-1	-2
Adverse effects that occurred statistically significantly more often with at least one of the SSRIs than with TCAs					
Nausea	+10*	+12*	+2*	+18*	+10*
Anorexia	+4*	+2	+2	+5*	+5*
Diarrhea	+5	+13*	+6	+8	+8*
Insomnia	+8*	0	0	+5	+4*
Nervousness	+3	+7*	-4	+2	+4*
Fatigue	-4	-10	+2*	-6	-2
Adverse effects for which there was a statistically significant difference (occurring more often with SSRIs than with the group of TCAs) only for pooled rates					
Agitation	+13	+7	+4	0	+6*
Anxiety	+4	+7	-1	-	+5*

Note: The entries in each of the columns headed by a specific drug name are from meta-analyses of trials of each of these SSRIs against any TCA. The entries in the final column are from meta-analyses of all of the trials of SSRIs against any TCA.

*Adverse event occurred statistically significantly more frequently with SSRI (positive value) or TCA (negative value). Based on pooled rate difference obtained by meta-analysis of randomized controlled trials.

tients, may be of clinical importance. Only 8 of the RCTs that reported rates of hypotension had more than 20 patients in each arm. Studies with 500 or more patients in each arm would be required to achieve statistical significance. In general, more systematic reporting of adverse effects is necessary to increase the precision of estimates of rate differences.

The reporting of adverse effects may be influenced by the way this reporting is done. Some methods (e.g., checklists) may result in an overestimation of adverse effects, if, for example, the patient is made to feel that such symptoms are acceptable. Our findings indicate that, for the 2 effects for which reporting methods were analysed, the differences between SSRIs and TCAs were the same regardless of which method was used to elicit information from patients.

With the exception of chloral hydrate or short-acting benzodiazepines given for insomnia and sleep disturbances (which was reported in 58% of the RCTs), none of the adverse effects were reported to necessitate additional pharmacotherapy. Other management strategies for these effects included eventual dose reductions, a change of the drug or discontinuation of the medication. Of the patients who discontinued SSRI treatment because of adverse effects, one-third suffered from nausea and gastrointestinal discomfort, and one-fifth from anxiety, agitation or nervousness. In comparison, one-third of the patients discontinuing TCA therapy as a result of adverse effects suffered from dry mouth, constipation or dizziness. It appears that the burden of adverse effects was similar for the 2 classes, although the specific adverse effects were different.

Limitations

This study was restricted to published trials. Only double-blind RCTs were included, so as to increase the quality and accuracy of the results. A "funnel plot" of the estimated differences in the size of therapeutic effect between the 2 drug classes showed that there was little publication bias.^{6,14}

It should be noted that the predominance of certain adverse effects, such as nausea with SSRIs and dry mouth with TCAs, may unblind the health care provider or an informed patient and consequently affect the quality of the RCTs.

There were other limitations. A "real" association, attribution or causal inference could not be easily established because end-points such as nausea, dry mouth or other adverse effects were not specified in detail before the individual trials commenced. Even with rigorous inclusion and exclusion criteria for the trials, the populations could be heterogeneous with respect to prior susceptibility, prior chemotherapy or other confounding

variables. Symptoms resembling the side effects caused by TCAs are common among depressed primary care patients before pharmacotherapy is started and generally remit with the depressive episode. Indeed, in some cases, placebo-treated patients presented some of these symptoms, though less often. Dry mouth may be induced by the pharmacotherapy, but it is also associated with a variety of clinical conditions that may go undiagnosed, including Sjögren's syndrome, diabetes, therapeutic radiation and psychogenic conditions, and in fact may be idiopathic. Most trials in which adverse effects were considered reported nothing more than rates: neither the intensity of the symptom nor the impact on the patient's quality of life was examined. Consequently, for example, attributing discontinuation solely to intolerable dry mouth or nausea may be speculative. Better study design and awareness of the somatic effects of major depression and of the consequences of therapy could result in better understanding and management of antidepressant pharmacotherapy by both physicians and patients.

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Appendix 1: Clinical trials comparing selective serotonin reuptake inhibitors with tricyclic antidepressants published between January 1980 and May 1996 and meeting the study criteria*†


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*Listed in alphabetical order according to first author's surname.

†See reference 6 for details on individual trial estimates.



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