New drugs with novel therapeutic characteristics

Have they been subject to randomized controlled trials?

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ABSTRACT

OBJECTIVE To determine how many randomized controlled trials on the safety or efficacy of new drugs are published when these drugs are first marketed in Canada, and to determine the quality of the information in those trials.

DESIGN A MEDLINE search was conducted on each drug identified as having novel therapeutic characteristics and first marketed between 1990 and 2000.

MAIN OUTCOME MEASURES Number of trials dealing with the safety or efficacy of each drug published at the time the drug was marketed. Number of patients taking the study drug, length of the trial, and type of control.

RESULTS The number of trials varied substantially. For some drugs, there were more than 20 studies; for others only a single study. Many trials were small and short-term, and used placebo controls.

CONCLUSION Too few trials or inadequate trials on the safety and efficacy of new drugs are published when these drugs are first marketed in Canada. The lack of published trials means that physicians do not know whether results are generalizable to their patients, how to position the drug in relation to other treatments, or whether the drugs have long-term safety and efficacy.

RÉSUMÉ

OBJECTIF Déterminer combien d'études randomisées sur l'innocuité et l'efficacité des nouveaux médicaments ont été publiées au moment de leur commercialisation au Canada et évaluer la qualité de l'information qu'on y trouve.

TYPE D'ÉTUDE Il s'agit d'une recherche dans MEDLINE pour identifier tout médicament doué de propriétés thérapeutiques nouvelles ayant été commercialisé pour la première fois entre 1990 et 2000.

PRINCIPAUX PARAMÈTRES MESURÉS Nombre d'essais publiés sur l'innocuité et l'efficacité de chaque médicament au moment de sa commercialisation. Nombre de patients ayant reçu le médicament étudié, durée de l'essai et type de groupe témoin utilisé.

RÉSULTATS Le nombre d'essais effectués était très variable. Pour certains médicaments, il y avait plus de 20 études alors que pour d'autres, il n'y en avait qu'une. Plusieurs essais portaient sur un petit nombre de sujets, étaient de courte durée ou avaient un groupe placebo comme témoin.

CONCLUSION On a constaté des carences dans le nombre et la qualité des études portant sur l'innocuité et l'efficacité des nouveaux médicaments qui sont parues avant la commercialisation de ces produits au Canada. À cause de ces carences, le médecin ignore si les résultats de ces essais sont applicables à ses patients, ne peut situer ce médicament par rapport aux autres modes de traitement, et n'est pas renseigné sur son innocuité et son efficacité à long terme.

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RESEARCH

New drugs with novel therapeutic characteristics

Information on new drugs appearing on the market is usually sparse. Health Canada bases its decisions on whether to approve new drugs on reports of randomized controlled trials (RCTs) dealing with these drugs' safety and efficacy that are submitted by manufacturers. Data from these trials, however, are confidential, and there is no guarantee they will ever be published. Promotional material from manufacturers is available, but can be biased.[1]

Physicians find the other main source of information, product monographs, difficult to use because these monographs are too long and poorly organized, and contain a great deal of information of little use to health professionals.[2] Published RCTs provide doctors with a source of independent information that helps them to prescribe new medications appropriately.

Most new drugs in Canada fall into one of two categories: modifications of existing drugs (eg, a combination of two active ingredients or an extended-release version of an immediate-release preparation) or additions to therapeutic classes (eg, a new β-blocker).[3] For these two categories, physicians can usually rely on the known characteristics of the already existing medications or therapeutic classes for prescribing the new products.

Some new drugs, referred to here as drugs with novel therapeutic characteristics, have active ingredients not related to those already on the market or work through novel therapeutic mechanisms. For these drugs, the situation is different because there are, by definition, no closely related products or therapeutic groups to use for reference. Reports have indicated that, when such drugs are marketed, there are few or no published RCTs available for doctors to consult.[4,5]

This study tried to determine whether there were published RCTs dealing with the safety or efficacy of drugs with novel therapeutic characteristics available when these drugs were first sold in Canada, and whether these trials contained certain important information that would allow physicians to prescribe the drugs appropriately.

METHODS

Every December, the magazine *Pharmacy Practice* publishes a list of the 200 drugs prescribed most frequently during the year and states the month and year when they were initially marketed. This information is supplied to *Pharmacy Practice* by International Medical Statistics (IMS) Health Canada, a major international supplier of information on pharmaceuticals.

Lists for the years 1992 to 2000 inclusive, with the exception of 1999 when the introductory month and year were not included, were manually searched for drugs with a single active ingredient that were first marketed between 1990 and 2000 inclusive. The active substance and mechanism of action of each drug were determined from the monograph in the *Compendium of Pharmaceuticals and Specialties* (CPS), and the Therapeutic Guide section of the CPS was consulted to see whether other related drugs were available.

Drugs were selected if they had novel therapeutic characteristics (ie, active substances not related to ones already on the market) or worked through novel therapeutic mechanisms. Salts, esters, and variations on dosage forms of existing drugs were excluded, as were combination products. For each drug selected, month and year of introduction were recorded.

For each drug, a MEDLINE search was conducted using the generic name of the drug with the limiters English language, human, and randomized controlled trial. The search covered the period from January 1966 to the end of the year in which the drug was introduced. A second search was then done for the same period using as subject heading(s) the indication(s) for each drug as stated in the official product monograph. These two searches were combined to yield a list of RCTs evaluating the drugs' safety and efficacy. Abstracts of citations were reviewed to ensure they were RCTs on the primary indication for the product and that they dealt with either efficacy or safety.

Trials on the intravenous form of drugs were excluded because intravenous drugs are primarily intended for use in hospitals. Studies done on groups of patients for whom these drugs did not have an official indication (eg, cisapride for children) were also excluded. Only trials published in full were included. Papers that presented the results of many RCTs were included if they contained methodologic details for each of the trials, but were rejected if they presented only results. Date of publication of each trial was noted; trials published up to 1 month before the drug was marketed were deemed to have been available when the drug was marketed.

For each trial, number of patients in the study arm, whether the trial had a placebo or active treatment

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control, and duration of the trial was extracted. These elements were chosen as proxies for the generalizability of trial results (number of patients taking the study drug), ability to position the drug with respect to other treatments for the same condition (active or placebo control), and long-term safety and efficacy (length of trial). A single person did the search and data extraction.

Letters were sent to each company producing the drugs in question to verify marketing dates and to determine whether there were additional trials not picked up in the MEDLINE search. A single reminder was sent to companies not responding within 5 weeks.

RESULTS

Fifteen drugs made by 12 different companies were identified. Bupropion was marketed for two separate indications, smoking cessation and depression, and, in each case, was a product with novel therapeutic characteristics. Therefore, it was included for each indication, giving a total of 16 products.

Ten companies marketing 14 drugs responded to the letter. In all cases companies confirmed the marketing date. In three instances, companies identified additional studies not found through the MEDLINE search.

Table 1 shows the number of RCTs published up to 1 month before each drug was marketed. The number was highly variable. For four products, there were three or fewer trials before they were marketed; for three others, there were more than 16 trials. Although there were four trials on celecoxib, they were all reported in a single publication.

Table 2 shows the characteristics of the RCTs that would make the available information helpful for prescribing physicians. There were many large studies (ie, more than 100 people receiving the study drug) for eight of the 16 products. For another four drugs, there was a single large trial. For cisapride, seven trials had fewer than 50 subjects, and the other two enrolled only 56 and 71 patients. For risperidone, 14, 21, and 92 patients received the drug in three trials. For zopiclone, seven of eight studies had fewer than 50 subjects in the treatment arm.

Information on comparison with other medications used for the same purpose was lacking for five drugs because all the trials were placebo controlled. Trials tended to be of relatively short duration. Trial duration was available for 129 RCTs: only 9% of RCTs lasted longer than 26 weeks, and more than 33% were shorter than 4 weeks.

For the four products for which there were three or fewer studies available at the time of launch (bupropion for smoking cessation, gabapentin, nefazodone, and olanzapine), information in the available trials was of variable usefulness. The single trial for bupropion was large (more than 100 patients) and lasted longer than 26 weeks, but was

Table 1. Number of randomized controlled trials available when drugs were first marketed

DRUG	INDICATION(S)	MONTH/YEAR FIRST MARKETED	NO. OF TRIALS PUBLISHED
Brimonidine	Glaucoma	12/1997	7
Bupropion	Depression	05/1998	21*
Bupropion	Smoking cessation	08/1998	1
Celecoxib	Osteoarthritis	04/1999	4
	Rheumatoid arthritis		
Cisapride	Gastrointestinal motility problems	01/1990	9
Gabapentin	Epilepsy	05/1994	3
Latanoprost	Glaucoma	07/1997	16
Losartan	Hypertension	10/1995	7
Montelukast	Asthma	08/1998	8
Nefazodone	Depression	05/1994	3
Olanzapine	Schizophrenia	11/1996	2
Orlistat	Obesity	05/1999	8*
Risperidone	Schizophrenia	05/1993	5
Sildenafil	Erectile disfunction	03/1999	10*
Sumatriptan	Migraine	02/1992	10*
Zopiclone	Hypnotic	08/1990	17

**Some papers reported results of more than one trial.*

Table 2. Characteristics of published randomized controlled trials of the safety and efficacy of new drugs

	NO. OF PATIENTS IN STUDY ARM			TYPE OF CONTROL			LENGTH OF TRIAL (WEEKS)			
DRUG	1-49	50-99	>100	ACTIVE	PLACEBO	ACTIVE AND PLACEBO	<1	1-3	4-26	>26
Brimonidine	0	0	7	3	4	0	3	0	2	2
Bupropion (depression)*	8	8	3	9	10	1	0	0	19	1
Bupropion (smoking cessation)	0	0	1	0	1	0	0	0	0	1
Celecoxib†	0	0	0	2	2	0	0	3	1	0
Cisapride	7	2	0	2	6	1	0	0	9	0
Gabapentin	1	1	1	0	3	0	0	0	3	0
Latanoprost‡	9	2	4	10	6	0	2	6	8	0
Losartan‡	2	0	4	4	1	2	0	0	7	0
Montelukast	3	1	4	0	8	0	2	2	4	0
Nefazodone‡	1	0	1	0	1	2	0	0	2	1
Olanzapine	1	0	1	0	1	1	0	0	2	0
Orlistat§	2	0	8	0	10	0	0	0	3	7
Risperidone‖	2	1	0	3	0	2	0	0	3	0
Sildenafil¶	6	0	4	0	10	0	2	2	6	0
Sumatriptan#	1	1	9	2	9	0	9	0	2	0
Zopiclone**	7	1	0	8	4	5	1	11	3	0

**Four trials reported in one paper, two trials reported in another paper; no. of patients not reported in two trials; type of control and duration of trial not reported in one trial.*
†Four trials reported in one paper; no. of patients in trials not reported.
‡No. of patients in one trial not reported.
§Two trials reported in one paper on two occasions.
‖Number of patients in trial and duration of trial not reported in two trials.
¶Two trials reported in one paper on three occasions.
#Two trials reported in one paper.
***No. of patients not reported in nine trials; duration of trial not reported in two trials.*

placebo controlled. Gabapentin had three short (4 to 26 weeks) trials of various sizes; all of them were placebo controlled. Nefazodone had one trial with 1 to 49 patients and one with more than 100 (the size of one trial was not given). Trials had both active and placebo controls. Two lasted between 4 and 26 weeks, and one lasted longer than 26 weeks. Finally, the two trials of olanzapine were both 4 to 26 weeks. One had an active control, and one had a placebo control. One was small (1 to 49 patients), and one was large (more than 100 patients).

DISCUSSION

This study shows that, for four of the 16 products (25%), three or fewer published RCTs were available at the time they were marketed. Even when there were RCTs, many of them were of short duration, enrolled small numbers of patients, and were placebo controlled. If only small numbers of patients have taken the drug (eg, the nine trials of cisapride included a total of only 254 subjects), physicians cannot be confident that their patients are appropriate candidates for the medication.

If drugs, such as sumatriptan, are meant for episodic use, short trials are justified. Other products, such as cisapride, losartan, and risperidone, are intended for chronic use, and the lack of trials lasting longer than 6 months might mean the long-term safety and efficacy are unknown. In the absence of active controls, how are physicians supposed to know where a drug like montelukast fits into the therapeutic spectrum of asthma medications or how bupropion compares with nicotine replacement therapy for smoking cessation?

These comments are not a criticism of the approval process undertaken by Health Canada nor of the adequacy of the material submitted to Health Canada. The clinical trials Health Canada uses to decide whether to allow a new drug on the market might or might not be the same as the ones eventually published. This paper is concerned only with the volume and quality of the material published and, therefore, available to clinicians.

Although RCTs do not necessarily give doctors all the information they need to use a drug appropriately, they are the criterion standard for information about the efficacy of medications.[6] Practising doctors sometimes do not read original medical literature when making decisions about prescribing new drugs. In the early stages, after a drug has been marketed, when postmarketing studies are not available and there is relatively little clinical experience, however, RCTs are still important for informing physicians about the new drugs. Talks at continuing medical education events and review articles not based on information from RCTs are liable to disseminate biased information. Therefore, the absence of RCTs would still limit physicians' ability to access the best-quality information. The lack of RCTs is especially worrisome for drugs that are not comparable to existing medications.

This study has some limitations. Selection of products was limited by the availability of data about introductory dates, but even if more drugs were included, the fact remains that, for four widely used medications, very little clinical information had been published when these products were marketed. Measures of the usefulness of information in the trials (number of patients receiving the study drug, type of control, and duration of trial) only have face validity; other types of information might be more valuable to doctors.

There are many reasons for the lack of published RCTs at the time of launch, including the publishing schedules of journals. Another source of clinical data could be in the information that companies submit to Health Canada in order to get products approved. In Canada, these data are regarded as confidential. Health Canada will release the information only with permission from the companies involved, and that permission is often not forthcoming. In contrast, in the United States, such data are made available under that country's Freedom of Information Act, regardless of whether companies cooperate.[7]

CONCLUSION

There is no reason that I can see for information that is readily accessible in the United States to be withheld in

Editor's key points

- Health Canada approves new medications on the basis of information supplied by the manufacturers, not all of which is released to the public. Published randomized controlled trials (RCTs) are the only reliable source of information on new drugs prescribing physicians can access.
- This study searched for published RCTs on innovative drugs when they were first marketed in Canada between 1990 and 2000.
- For 16 new products, the number of published RCTs varied widely: six products had nine or more trials, but four had three or fewer. Some trials had relatively small numbers of patients and others were of short duration. Some were only placebo-controlled rather than compared with other active drugs.
- Additional information would be available to physicians if Health Canada were allowed to release manufacturers' data on new drugs, as the government does in the United States.

Points de repère du rédacteur

- Santé Canada approuve les nouveaux médicaments en se basant sur les informations fournies par les manufacturiers, mais celles-ci ne sont pas toutes rendues publiques. Les articles rapportant les essais randomisés de ces produits constituent donc la seule source de renseignements valable pour le médecin qui envisage de les prescrire.
- Dans la présente étude, on a recensé les articles portant sur les essais randomisés des médicaments doués de propriétés thérapeutiques nouvelles et dont la commercialisation a été approuvée pour la première fois entre 1990 et 2000.
- Le nombre de publications rapportant des essais randomisés variait beaucoup selon les médicaments: six des 16 nouveaux produits étudiés avaient au moins neuf essais, mais quatre n'en comptaient que trois ou moins. Certains de ces essais portaient sur un nombre relativement restreint de patients et d'autres étaient de courte durée. Dans certains cas, la comparaison était faite avec un groupe placebo plutôt qu'avec un groupe recevant un médicament d'efficacité reconnue.
- Les médecins canadiens seraient mieux informés si le gouvernement canadien imitait celui des États-Unis et permettait à Santé Canada de diffuser les données qu'il reçoit des manufacturiers concernant les nouveaux médicaments.

Canada. Health Canada needs to reconsider its policy of keeping clinical data confidential so that necessary information can be made available to clinicians in a timely fashion. Such a change in policy would be in line with recommendations made to Health Canada by its own Science Advisory Board in February 2000.[8]

For many new drugs, there are few published RCTs when these drugs are first marketed in Canada. Even when RCTs are available, they sometimes do not contain enough information to help clinicians to use the drugs appropriately. Placebo controls, rather than active controls, are often used; trials are of short duration for drugs meant to be taken long-term, and many trials enrol small numbers of patients.

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References

1. Wilkes MS, Doblin BH, Shapiro MF. Pharmaceutical advertisements in leading medical journals: experts' assessments. *Ann Intern Med* 1992;116:912-9.
2. Gagnon D. *Working in partnerships. Drug review for the future*. Ottawa, Ont: Department of Health and Welfare; 1992.
3. Patented Medicine Prices Review Board. *Tenth annual report: for the year ended December 31, 1997*. Ottawa, Ont: Supply and Services Canada; 1998.
4. Melzer D. New drug treatment for Alzheimer's disease: lessons for healthcare policy. *BMJ* 1998;316:762-4.
5. Gale EA. Lessons from the glitazones: a story of drug development. *Lancet* 2001;357:1870-5.
6. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? *N Engl J Med* 2000;342:1907-9.
7. Lexchin J. Secrecy and the Health Protection Branch. *Can Med Assoc J* 1998;159:481-3.
8. Science Advisory Board, Health Canada. *Report of the Committee on the Drug Review Process*. Ottawa, Ont: Health Canada; 2000.