BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2008.03342.x

The use and potential abuse of anticholinergic antiparkinson drugs in Norway: a pharmacoepidemiological study

Pål Gjerden, Jørgen G. Bramness[1] & Lars Slørdal[2]

Department of Psychiatry, Telemark Hospital, Skien, [1]Department of Pharmacoepidemiology, Norwegian Institute of Public Health, Oslo and [2]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway

Correspondence
Dr Pål Gjerden, Department of Psychiatry, Telemark Hospital, N-3710 Skien, Norway.
Tel: + 47 3500 3476
Fax: + 47 3500 3187
E-mail: pal.gjerden@sthf.no

Keywords
adverse effects, anticholinergic agents, antiparkinson agents, antipsychotic agents, drug abuse

Received
9 June 2008

Accepted
18 October 2008

Published *Early View*
16 December 2008

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Anticholinergic antiparkinson drugs are used to ameliorate extrapyramidal symptoms caused by either Parkinson's disease or antipsychotic drugs, but their use in the treatment of Parkinson's disease is assumed to be in decline.
- Patients with psychotic conditions have a high prevalence of abuse of drugs, including anticholinergic antiparkinson drugs.

WHAT THIS STUDY ADDS

- Anticholinergic antiparkinson drugs in Norway were primarily prescribed to patients using antipsychotic medication.
- The risk of abuse of this group of drugs was small, even among patients who probably abused other drugs.

AIMS

The use of anticholinergic antiparkinson drugs is assumed to have shifted from the therapy of Parkinson's disease to the amelioration of extrapyramidal adverse effects induced by antipsychotic drugs. There is a considerable body of data suggesting that anticholinergic antiparkinson drugs have a potential for abuse. The aim was to investigate the use and potential abuse of this class of drugs in Norway.

METHODS

Data were drawn from the Norwegian Prescription Database on sales to a total of 73 964 patients in 2004 of biperiden and orphenadrine, and use in patients with Parkinson's disease or in patients who were also prescribed antipsychotic agents. Possible abuse of these drugs was assessed by the level of use, skewedness of use, indications of drug-seeking behaviour and concomitant use of benzodiazepine tranquillizers, a group of prescription drugs with a recognized potential for abuse.

RESULTS

Anticholinergic antiparkinson drugs were prescribed to 4.5% of all outpatients who used antipsychotic drugs. This outnumbered sales to patients with Parkinson's disease by >20 to 1. We found indications of abuse of benzodiazepine tranquillizers among patients using antipsychotics, but there were no clear indications of abuse of anticholinergics, even among patients who were strongly suspected of abuse of benzodiazepines.

CONCLUSIONS

Anticholinergic antiparkinson drugs were used primarily by patients with psychotic illnesses. These patients have a very high prevalence of legal and illegal drug abuse, but the risk of abuse of anticholinergic antiparkinson drugs seemed small.

Introduction

The first anticholinergic antiparkinson drugs were synthesized in the 1940s. Until the introduction of levodopa they were the mainstay of Parkinson's disease treatment. Their primary use now is assumed to be the amelioration of extrapyramidal adverse effects induced by antipsychotic medication, but there is not much documentation thereof. One of these anticholinergic agents, orphenadrine, has also been used as a muscle relaxant [1] and a pain killer [2, 3], but these indications were not approved in Norway at the time of our study. There have been reports of misuse of anticholinergic agents since the 1980s, but the reported prevalence varies considerably, up to 34% in relevant patient groups [4].

When introduced, these drugs were not subject to comprehensive premarketing evaluations. Little information is available for either of the anticholinergic antiparkinson compounds marketed in Norway at the time of this study, biperiden and orphenadrine. Pharmacokinetic data are largely restricted to studies involving healthy volunteers given single doses [5]. Orphenadrine in particular has a complex metabolism, with one of its metabolites acting as an autoinhibitor, causing unexpectedly high blood levels of the parent compound with continuous as opposed to single-dose use [6]. These two agents are also different from a pharmacodynamic perspective; orphenadrine is a derivative of the first-generation antihistamine diphenhydramine and confers a wide range of effects in addition to muscarinic cholinoceptor blockade, whereas biperiden resembles the classical anticholinergic compound atropine [7].

In 1998, we identified more than 80 reported deaths following orphenadrine overdoses in the literature [8], and reported 21 deaths over an 11-year period in Norway [9]. The high fatality rate linked to orphenadrine has subsequently been confirmed by others [10]. Especially noteworthy are the low doses that sometimes cause lethal intoxications and the short time span between exposure and death. By contrast, there are no reports in the literature of deaths due to overdose of biperiden. Orphenadrine was withdrawn from the Scandinavian market in 2005 but is still marketed in many parts of the world, including the UK, USA and Canada. It is available as an over-the-counter drug in some countries. Its use in connection with euthanasia in the Netherlands [11] is a thought-provoking contrast to this practice.

The abuse potential of medicinal drugs is difficult to assess in premarketing studies [12]. A prescription database allows the possibility of postmarketing surveillance of patterns of drug use [13, 14]. Several different parameters indicating drug abuse on the basis of prescription data have been assessed. In the absence of other explanations, extensive use and skewed distribution of drug use can indicate abuse [15]. Other caveats include doctor shopping, i.e. the sequential consulting of different doctors to obtain prescriptions, and the concomitant use of other prescription drugs with a recognized potential for abuse [16].

The aim of this study was to gain information about the use of biperiden and orphenadrine in Norway and explore possible cases of abuse by investigating prescriptions given to individual patients, with an emphasis on the differences between the drugs.

Materials and methods

Prescription database

The Norwegian Prescription Database (NorPD) contains information on all drugs prescribed to individual patients living outside institutions from 1 January 2004. It covers the entire population of 4.6 million inhabitants [17]. The data collected and used in this study are: patients' unique identifiers (encrypted), gender, age, date of dispensing and drug information (brand name, package size, number of packages, Anatomical Therapeutic Chemical classification code (ATC code) and defined daily dose (DDD), i.e. the assumed average maintenance dose per day for a drug used for its main indication in adults [18]). If the drug is reimbursed by the government, as it will be if it is used for a chronic condition like idiopathic Parkinson's disease or a psychotic condition requiring long-term medication, a reimbursement code will also be noted. This code will indicate whether the drug is prescribed for Parkinson's disease or a serious psychiatric condition.

Study population

Potential indications for the use of anticholinergic antiparkinson drugs are either adverse effects caused by antipsychotic drugs, primarily parkinsonian symptoms, or Parkinson's disease, or both at the same time. Data were drawn from the NorPD for the year 2004 for patients from 18 to 69 years of age. The total amounts of biperiden, orphenadrine and benzodiazepines prescribed as tranquillizers were noted for four subgroups: (i) patients using any antipsychotic drug, (ii) patients assumed to be suffering from idiopathic Parkinson's disease either because they used a dopaminergic antiparkinson drug or because they were prescribed anticholinergic antiparkinson drugs that were reimbursed for Parkinson's disease, (iii) patients with Parkinson's disease who were also using an antipsychotic drug, and (iv) patients who neither had Parkinson's disease nor were prescribed antipsychotic medication, but were using anticholinergic drugs off-label. At the time of the study only three benzodiazepines were marketed as tranquillizers in Norway: diazepam, oxazepam and alprazolam. A small number of patients using lorazepam, bromazepam or clobazam (10, one and 19 patients, respectively) were also included. Fifteen patients (five from Group 1, three from Group 2 and seven from Group 4) using either

trihexylphenidyl/benzhexol or procyclidine, two anticholinergic antiparkinson drugs not marketed in Norway at the time of the study, were excluded.

Pharmacoepidemiological parameters

One-year prevalence of use of antipsychotic drugs and concomitant use of anticholinergics and benzodiazepine tranquillizers was defined as the number of individuals who had received at least one prescription for an antipsychotic drug, biperiden or orphenadrine, or a tranquillizer in 2004. One-year prevalence of patients with Parkinson's disease using antiparkinson medication was defined as the number of patients who had received at least one prescription for a dopaminergic antiparkinson drug or at least one prescription for an anticholinergic antiparkinson drug where idiopathic Parkinson's disease was noted as the indication for the prescription. All patients were identified by age and gender.

The level of drug use was studied by assessing the mean amount in DDD of biperiden or orphenadrine prescribed to individual patients in the year 2004. The DDD of biperiden and orphenadrine are 10 mg and 200 mg, respectively. The level of concomitant use of benzodiazepines was noted as the sum of DDDs of diazepam equivalents (1 diazepam equivalent = 10 mg diazepam = 30 mg oxazepam = 1 mg alprazolam = 2.5 mg lorazepam = 10 mg bromazepam = 20 mg clobazam).

We also assessed several parameters from the NorPD that could indicate abuse of anticholinergic antiparkinson drugs. We found Lorenz curves useful as graphical representations of possible skewedness of drug use patterns, with Lorenz 1% figures representing the percentage of the total amount of drugs being used by the highest drug-consuming 1% of the population. A figure exceeding 15% is considered a strong indicator that the drug in question is being abused [15, 16]. Lorenz 50% figures represent the percentage of the total amount of drugs being used by the highest drug-consuming half of the population, whereas the Gini coefficient is the difference in percentage between areas delineated by the observed distribution curve and a perfect equality line of 45°. In both instances, higher numbers indicate more skewed use. We calculated Lorenz curve parameters for anticholinergics and tranquillizers among antipsychotic users and likewise for the total use of biperiden, orphenadrine and tranquillizers. The number of patients in the other three study groups was too small for Lorenz curve calculations.

Doctor shopping was investigated by noting the number of doctors concomitantly prescribing tranquillizers to each patient, whether the patient had used the services of more than three doctors for such prescriptions and the maximum number of doctors involved for each patient. The number of anticholinergic drug users was so small that corresponding indicators for doctor shopping for this group did not give meaningful information. The statistical software used was SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the number of patients in each of the four groups, including the subgroups using either biperiden or orphenadrine as concomitant medication. Use of anticholinergics and benzodiazepine tranquillizers is also shown. Some patients were prescribed more than one anticholinergic agent; one patient used biperiden and procyclidine and 77 patients used both biperiden and orphenadrine during the year 2004, but not necessarily at the same time.

The main consumers of anticholinergic antiparkinson drugs were patients using antipsychotic medication, outnumbering patients suffering from Parkinson's disease by more than 20 to 1. Patients using antipsychotic drugs accounted for 94.0% of the use of anticholinergics, compared with 4.3% with Parkinson's disease. Patients who both had Parkinson's disease and were recipients of prescriptions for antipsychotics accounted for 0.4% of the use of anticholinergics, whereas patients with neither accounted for 1.3%. Only 4.5% of all patients using antipsychotic medication and 5.3% of patients with Parkinson's disease were also dispensed anticholinergic drugs. There was a tendency for Parkinson's disease patients to be older than the other patients, reflecting the fact that Parkinson's disease principally affects individuals beyond middle age. The gender ratio was comparable in all four groups.

The overall use of anticholinergics was not very high. The frequency of use of benzodiazepine tranquillizers was higher among patients using antipsychotics than among those with Parkinson's disease, but patients who neither used antipsychotics nor had Parkinson's disease—but nevertheless used biperiden—had the highest concomitant use of benzodiazepines of all.

Lorenz curves for anticholinergics and benzodiazepine tranquillizers for patients using antipsychotic medication, accounting for 70 937 of a total of 73 964 patients, are shown in Figure 1. The corresponding Lorenz curve figures are given in Table 2. Lorenz curve 1% figures for benzodiazepines were higher for patients using antipsychotics only (but not anticholinergics) than for those using both.

We also calculated Lorenz curve figures for all patients in the four subgroups taken together for benzodiazepine tranquillizers, biperiden and orphenadrine. Lorenz curve 1% figures for biperiden, orphenadrine and benzodiazepines were, 6.2, 5.4 and 16.5, respectively.

The four groups did not differ significantly regarding the number of prescribing doctors or cases where there were three or more prescribing doctors for benzodiazepine tranquillizers. The maximum number of benzodiazepine-prescribing doctors for the four groups was eight, five, three and six, respectively. These data are not shown in the tables.

Table 1

Pharmacoepidemiological data for the four user groups of anticholinergic agents (Norwegian Prescription Database 2004)

	n (% of whole group)	Age Mean (SD)	Female gender *n* (%)	Use of anticholinergics (DDD/year) Mean (SD)	Number of users of benzodiazepine tranquillizers *n* (%)	Diazepam equivalents (DDD/year) Mean (SD)
Group 1: users of antipsychotics						
***n* = 70 937**						
Using antipsychotics, but no anticholinergics	67 840 (95.6)	46.4 (13.2)	37 203 (54.8)		22 324 (32.9)	211.7 (406.9)
Using antipsychotics and biperiden	2 083 (2.9)	48.6 (11.5)	1 002 (48.1)	114.7 (109.1)	895 (43.0)	248.3 (344.7)
Using antipsychotics and orphenadrine	1 090 (1.5)	50.0 (11.3)	571 (52.4)	157.6 (134.7)	378 (34.7)	264.4 (387.0)
Group 2: patients with Parkinson's disease						
***n* = 2771**						
Parkinson's patients without anticholinergics	2 626 (94.8)	58.5 (9.4)	1 139 (43.4)		518 (19.7)	110.5 (159.4)
Parkinson's patients using biperiden	104 (3.8)	52.0 (10.7)	51 (49.0)	108.1 (112.3)	37 (35.6)	209.5 (346.4)
Parkinson's patients using orphenadrine	42 (1.5)	57.3 (9.1)	25 (59.5)	191.5 (146.2)	15 (35.7)	147.9 (158.3)
Group 3: patients with Parkinson's disease also using antipsychotics						
***n* = 213**						
Patients with Parkinson's disease also using antipsychotics	201 (94.4)	59.8 (10.2)	91 (45.3)		87 (43.3)	186.7 (211.5)
Patients with Parkinson's disease also using antipsychotics and biperiden	8 (3.8)	60.3 (8.7)	3 (37.5)	155.0 (120.4)	4 (50.0)	196.9 (63.1)
Patients with Parkinson's disease also using antipsychotics and orphenadrine	4 (1.9)	63.8 (5.3)	2 (50.0)	143.8 (100.8)	2 (50.0)	540.0 (339.4)
Group 4: users of anticholinergics not using antipsychotics or having Parkinson's disease						
***n* = 43**						
Biperiden	31 (72.1)	49.2 (13.3)	14 (45.2)	59.7	16 (51.6)	629.6 (1 080.4)
Orphenadrine	12 (27.9)	45.0 (15.8)	7 (58.3)	31.3	2 (16.7)	32.5 (10.6)

Table 2

Lorenz curve parameters for patients using antipsychotic medication. All figures are percentages

	Anticholinergic antiparkinson drugs			Benzodiazepine tranquillizers		
	Lorenz 1%	Lorenz 50%	Gini coefficient	Lorenz 1%	Lorenz 50%	Gini coefficient
Antipsychotics without anticholinergics				14.3	93.7	67.9
Antipsychotics + biperiden	6.5	81.6	45.1	9.8	90	59.2
Antipsychotics + orphenadrine	5.6	78.3	41.1	10.2	90.2	60.5

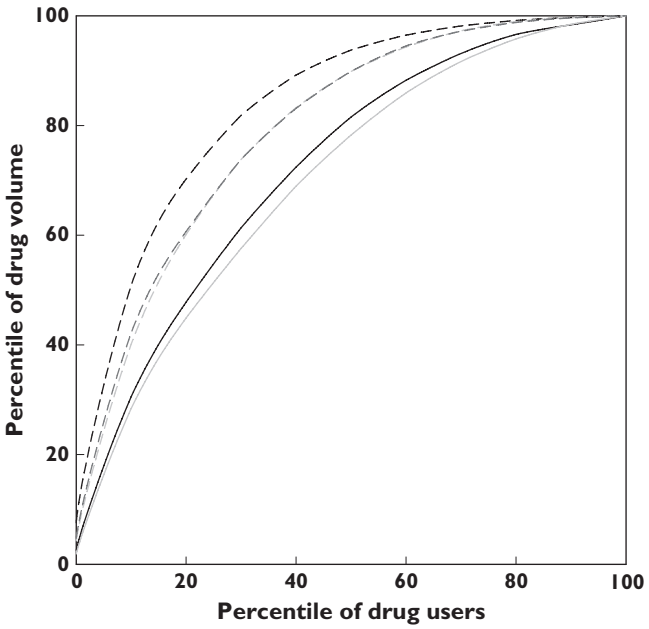

Figure 1

Lorenz curves for patients using antipsychotic medication. The graph shows the proportion of drug use that is accounted for by the percentiles of drug users. Biperiden (——); Orphenadrine (——); Benzodiazepines in non users of anticholinergics (– – –); Benzodiazepines in biperiden users (– – –); Benzodiazepines in orphenadrine users (– – –)

Discussion

The study has demonstrated that about 5% of patients either using antipsychotic medication or suffering from Parkinson's disease were prescribed anticholinergic antiparkinson drugs. The use of anticholinergics in Norway was almost exclusively confined to users of antipsychotics, probably to treat extrapyramidal side-effects caused by the latter group of drugs. Overall, biperiden was prescribed twice as often as orphenadrine. We could not find strong pharmacoepidemiological signs of abuse of anticholinergic antiparkinson agents. The level of use of both biperiden and orphenadrine was comparably low in all groups.

The use of biperiden and orphenadrine was not particularly skewed. Lorenz curve parameters did not indicate drug abuse, nor did doctor shopping parameters. However, we were able to demonstrate indications of benzodiazepine abuse in the study group. The overall Lorenz 1% figure of 16.5% strongly suggested abuse of benzodiazepines, as did the Lorenz 1% figure of 14.3% for patients who were using antipsychotics but not anticholinergics. We expected to find some abuse of anticholinergic drugs among patients who were using anticholinergics off-label, but this assumption could not be verified. The high level of benzodiazepine use among patients using biperiden off-label suggests that this group included a number of benzodiazepine-abusing patients, but extensive use of benzodiazepines coincided with a low level of biperiden use. A combined product of orphenadrine and paracetamol (acetaminophen) was marketed as a pain killer in Norway until 1996. The off-label use of orphenadrine could include a few patients who previously used orphenadrine for this indication.

A considerable proportion of patients used higher doses of benzodiazepine tranquillizers when they were given anticholinergics concomitantly. This could be interpreted as an indication of abuse, but it could just as well be an example of confounding by severity of disease; the most severely ill patients were given the most medication, both antipsychotics, leading to more anticholinergics, and benzodiazepines.

The use of benzodiazepine tranquillizers among patients using antipsychotic drugs was higher than among patients suffering from Parkinson's disease. This is hardly surprising given that the main indications for benzodiazepine use are mental symptoms. Benzodiazepines may even be used for some of the same adverse affects as anticholinergics are, and especially in akathisia, although the effect is not well documented [19]. The use of biperiden among patients using antipsychotic drugs seemed to coincide more often with the use of benzodiazepine tranquillizers than in the orphenadrine group (43.0% *vs.* 34.7%), but the level of benzodiazepine use was lower, yielding mixed arguments for a potential difference in the risk of abuse of biperiden *vs.* orphenadrine.

This study was able to collect information on the entire group of patients outside of mental institutions, making the study group both large and representative. Nevertheless, some subgroups of patients were too small to be eligible for statistical calculations. The disadvantages of this approach to the study of drug use include the limited amount of information that can be gathered on each patient, includ-

ing the severity of the condition, and lack of information as to whether prescribed drugs are actually consumed.

Patients suffering from psychotic conditions have a well-known risk of abuse of both legal and illegal substances, with a lifetime prevalence of drug abuse in schizophrenia approaching 50% [20–22]. There has been considerable fear of inducing drug dependence by giving anticholinergic drugs to patients with extrapyramidal adverse effects caused by antipsychotic medication. Earlier studies have reported prevalence rates of anticholinergic drug abuse between nil [23] and 18% [24–26], one study reporting an unprecedented high of 34% [4]. All of these studies have been conducted with seriously ill schizophrenic patients, the inclusion criterion being the diagnosis and not merely the use of antipsychotics. This makes it difficult to differentiate between the effect of anticholinergic drugs and the effects of the disease. In our study we tried to assess the use of anticholinergic antiparkinson drugs related to antipsychotic medication more directly.

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