Benzodiazepine and cyclopyrrolone reduction in general practice — Does this lead to concomitant change in the use of antipsychotics? A study based on a Danish population

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Article info

Introduction: In the period 2004–2006, 15 doctors in the Danish municipality of Lemvig introduced a more restrictive approach to the prescription of benzodiazepines and cyclopyrrolones. A prescription could be renewed only following personal consultation, and prescriptions were issued for only a single month’s usage. The intervention reduced the prescription of benzodiazepine anxiolytics by 50%, cyclopyrrolones by 57% and benzodiazepine hypnotics by 55% over a 1½ year period. There is a paucity of knowledge about whether such an intervention reduces drug consumption in general or merely shifts consumption to other drugs. Here especially antipsychotics (AP) are in the spotlight.

Materials and methods: The current article describes the prescription of antipsychotics before and after the intervention. Consumption was followed via the Danish Medicines Agency’s website Ordiprax, where the quantity of pharmacy-sold prescription drugs by individual medical practices can be monitored.

Results: The overall increase in the prescription of antipsychotics during the intervention described here was not more than 3.1% of the reduction in prescriptions of benzodiazepine and cyclopyrrolone measured in defined daily doses (DDD).

Conclusion: The intervention against benzodiazepine and cyclopyrrolone did not result in an uncontrollable increase in the prescription of antipsychotic drugs. It cannot be excluded that the intervention impacted individual prescriptions. For future interventions of a similar nature, it is recommended that GPs are trained in the use of antipsychotics.

Keywords: Benzodiazepines, Cyclopyrrolones, Antipsychotics, Sedative, Hypnotics, General practice

Benzodiazepines were introduced in 1960 as a successor to the barbiturates, chloral hydrate and meprobamate (Lader, 1991; Anonymous, 2009a). Specific advantages include their low toxicity and broad therapeutic application. It is now recognized that there are significant problems associated with the use of benzodiazepines and cyclopyrrolones. They may give rise to strong dependence with a pronounced tolerance development (Srisurapanont et al., 2006; Anonymous, 1980). Their hypnotic effect disappears after a few months, while their anxiolytic effect has almost disappeared after a few months (Srisurapanont et al., 2006; Anonymous, 1980). Accordingly, patients are consuming medicines which have no positive effect in long-term treatment.

In Denmark 8.2% of the population were users of benzodiazepines and cyclopyrrolones in 2008 (Gesser, 2009). The problem is not only Danish, and the number of users in, for example, Ireland and Spain is 25% and 18% of the population respectively. In Norway the corresponding figure is 6.5% of the adult population (Anonymous, 2001). In Denmark it is estimated that around 2% of the population is dependent on these substances (Hansen and Helweg-
The rules for the prescription of benzodiazepines and cyclopyrrolones are almost identical in, for example, England, Norway and Denmark (Anonymous, 2001, 2004, 2008). Benzodiazepines and cyclopyrrolones should only be prescribed for a few weeks, after which a re-evaluation must take place. These rules of good clinical practice were first advocated in 1988 in a Bulletin of the Royal College of Psychiatrists (Priest and Montgomery, 1988). However, no methods for implementation where indicated, and the scientific basis for the effectiveness of these rules was nonexistent.

In 2003, doctors at two medical practices in the Danish village of Thyborøn chose to address the issues (Jørgensen et al., 2006a,b; Jørgensen and Toft, 2008; Jørgensen, 2009). In collaboration with the Medicine Unit of Ringkjøbing County and the County Medical Health Officer, a few simple rules were introduced in the two practices for the prescription of benzodiazepines and cyclopyrrolones, including:

- the discontinuation of telephone prescriptions
- prescription only following personal consultation
- prescription for a maximum of 1 month's consumption

The intervention led to the patient and the doctor re-evaluating on a monthly basis whether current prescription levels were appropriate and therefore should continue, or whether a reduction should be initiated.

In a 3 1/4 year period from 2004, the two practices achieved a significant reduction in the prescription of benzodiazepine anxiolytics by 85%, of cyclopyrrolones by 91% and of benzodiazepine hypnotics by 83% (Jørgensen, 2009). The remaining doctors in the municipality were inspired, and subsequently introduced similar rules in their practices. One and a half years after the joint implementation of the rules, prescriptions of benzodiazepine anxiolytics were reduced by 50%, cyclopyrrolones by 57% and benzodiazepine-hypnotics by 55% (Jørgensen, 2007, 2010). The overall reduction of benzodiazepines and cyclopyrrolones was 2395 DDD / 1000 patients (Jørgensen, 2010).

Among colleagues it was argued that consumption was probably just transferred to antipsychotics instead. This objection is academically relevant, as it is known that other interventions of a similar nature have lead to a shift in the consumption of other drugs (Weintraub et al., 1991). The use of antipsychotics for anxiety disorders are generally considered to be scientifically poorly elucidated (Anonymous, 2007). In Denmark antipsychotics have occasionally been used for the treatment of anxiety disorders.

This article seeks to illuminate the issue of whether an intervention as described above leads to an actual reduction in benzodiazepine and cyclopyrrolone consumption or merely shifts consumption to other drugs, and the article focuses on changes in the prescription of antipsychotics following a systematic review of the group. The article also aims to strengthen the basis for decision-makers in health systems who work with addictive medication, as well as being an inspiration to fellow practitioners.

1. Materials and methods

Data were obtained from 15 general practitioners, covering 12 medical practices in the Danish municipality of Lemvig. Doctors had a patient base of approximately 20,830 patients, of which approximately 1000 patients participated in the intervention (Jørgensen and Toft, 2008). All practices participated in the intervention against the overuse of benzodiazepines and cyclopyrrolones. The two primary practices initiated the intervention in 2004 and the remaining 10 practices followed after the second quarter of 2005. The practices’ results are calculated as the average quarterly prescription in the years preceding the intervention, followed by prescription six quarters later.

The data compiled here are grouped according to their Anatomical Therapeutic Chemical (ATC) codes (Table 1). The groups give a complete overview of antipsychotics registered in Denmark, and are included for the sake of completeness, without considering their direct relevance and usefulness as substitutes for benzodiazepines and cyclopyrrolones.

The internet site http://www.Ordiprax.dk was used for evaluation (Anonymous, 2009b), since data were easily available and covers the desired material.

The Ordiprax data base comprises data reported by pharmacists to the Danish Medicines Agency Pharmaceutical Statistics Register for the sale of prescription drugs to individuals, registered as number of defined daily doses (DDD).

The average of the prescribed volume of antipsychotics in the four quarters preceding the intervention, is termed pre-intervention (“Before”). In practices 1 and 2, “Before” data covers the year 2003, and for the other practices the period from the second quarter of 2004 to first quarter of 2005. The average of the prescribed volume of antipsychotics six quarters after the initiation of the intervention is termed post-intervention (“After”). In practices 1 and 2 this covers the second quarter of 2005, and the third quarter of 2006 for the other practices. The total prescribed volume as well as the prescribed volume of all of the subgroups was evaluated.

In order to facilitate comparison with data from the rest of the country, gender and age-standardized data were chosen and no specific information on antipsychotics was given to patients, or to the staff of the participating physicians, and no unusual prescription initiatives in this area were implemented.

The annual average increase in the prescription of antipsychotics for the county was calculated on the basis of quarterly figures from 2003 to 2006. County prescription levels are illustrated through the use of a bar chart with error bars indicating the least significant difference (LSD), \( p = 0.05 \) calculated using analysis of variance (ANOVA) followed by the Student–Newman–Keuls post-ANOVA test.

2. Results

2.1. County results

The county prescription of antipsychotics increased by 3.7% per year on average during the period 2003–6. The increase was statistically significant (see Fig. 1). At the national level, the increase during the period 2005–6 was 2%.
The overall municipal increase in the prescription of antipsychotics during the intervention was 12.4%, representing an annual increase of 8.2%. The numerical increase was 76 DDD/1000 patients per quarter. This is considerably larger than the statistically significant increase at the county level of 3.7% per year during the intervention period. However this amount corresponds to less than one patient having been treated with 1 DDD/1000 patients per quarter. This should also be compared to the fact that the overall reduction in the prescription of benzodiazepines and cyclopyrrolones was 2395 DDD/1000 patients per quarter.

Each practice had differences in the prescription of antipsychotics ranging from 194 to 2474 DDD/1000 patients per quarter at initiation of the intervention. Six quarters after the initiation the differences ranged from 178 to 2669 DDD/1000 patients per quarter. There were also considerable differences in the percentage change in prescriptions, these ranged from a decline of 32% to an increase of 70%. Practice 33 was assigned to the area’s only psychiatric institution (Fig. 2).

The changes in prescriptions within the individual subgroups are shown in Fig. 3. During the initiative the groups N05AF and N05AX showed marked changes. The other groups had only minor variations in prescriptions.

In the group N05AF prescription decreased by 37%, equivalent to 1151 DDD throughout the municipality, corresponding to 55 DDD per 1000 patients. This group comprises first generation antipsychotics. At the national level, prescription in this group is also declining.

Group N05AX consists of second generation antipsychotics and shows a numerical increase of 2105 DDD throughout the municipality, representing an increase of 167%. The corresponding result is 101 DDD/1000 patients per quarter. At the national level, a marked increase in prescription also took place within this group.

3. Discussion

A Danish study from 2003 reveals that 12% of patients undergoing a reduction in their prescriptions of benzodiazepine were prescribed an alternative nerve medicine, including a significant proportion of antipsychotics (The Danish Medicines Agency, 2010).

The overall municipal increase in the prescription of antipsychotics during the intervention was 12.4%, representing an annual increase of 8.2%. The corresponding numerical increase was 76 DDD/1000 patients per quarter. This is considerably larger than the statistically significant increase at the municipality level of 3.7% per year during the intervention period. However this amount corresponds to less than one patient having been treated with 1 DDD/1000 patients per quarter. This should also be compared to the fact that the overall reduction in the prescription of benzodiazepines and cyclopyrrolones was 2395 DDD/1000 patients per quarter (Jørgensen, 2010). Thus, the increase in prescription of antipsychotics was merely 3.1% of the reduction in prescriptions of benzodiazepines and cyclopyrrolones measured in DDD.

This increase in the prescription of antipsychotics is mainly ascribed to the N05AX group, comprising Risperidone (risperdal, ridal) and Aripiprazole (abilify). Both are second generation antipsychotics and are generally regarded to be at least as effective as first generation antipsychotics, and are much better tolerated with fewer side effects. This group is increasingly prescribed by local psychiatrists. The N05AF group comprising Flupentixol (fluanxol, depixol, emergil) Chlorprothixene (truxal, taractan) and Zuclopenthixol (cisor-dinol, clopixol, acuphase) are first generation antipsychotics, and their use is decreasing. This is consistent with the general national trend (Anonymous, 2009b), which is to replace the older first generation antipsychotics with more modern, second generation antipsychotics having fewer side effects. The prescription of Flupentixol is declining in spite of the fact

### Table 1

The classification of antipsychotics after the Anatomical Therapeutic Chemical Classification System (ATC)-codes.

<table>
<thead>
<tr>
<th>3rd level</th>
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<tbody>
<tr>
<td>N05A</td>
<td>Antipsychotics</td>
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<tr>
<td>N05AA</td>
<td>Phenothiazines with aliphatic side chains</td>
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<td>Chlorpromazine</td>
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<td>Acepromazine</td>
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<td>N05AB</td>
<td>Phenothiazines with piperazine structure</td>
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<td>N05AC</td>
<td>Phenothiazines with piperidine structure</td>
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<td>Perciazine</td>
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<td>Thoridazine</td>
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<td>Benzamides</td>
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<td>Butyrophenone derivatives</td>
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<td>Haloperidol</td>
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<td>Melperon</td>
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<td>Pipamperone</td>
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<td>N05AF</td>
<td>Diazepins and oxazepines</td>
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<td>Clozapine</td>
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<td>Olanzapine</td>
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<td>Quetiapine</td>
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<td>N05AK</td>
<td>Neuroleptica for tardive dyskinesia</td>
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<td>Phenytoxine derivatives</td>
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<td>N05AH</td>
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<td>Aripiprazole</td>
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2.2. Municipality results

In Lemvig municipality the average prescription of antipsychotics in 2003 was 65% of county prescription levels at initiation of the intervention.

The overall increase in the prescription of antipsychotics during the intervention was 12.4%, which represents an annual increase of 8.2%. The numerical increase was 76 DDD/1000 patients per quarter, representing an annual increase of 8.2%. The corresponding numerical increase was 76 DDD/1000 patients per quarter.
that is has, to some extent, been prescribed for anxiety disorders. The N05AF group is mostly prescribed by psychiatrists, and general practices are usually responsible for prescription renewals. For the remaining groups of antipsychotics, changes in prescription volumes are so small that they are judged to be irrelevant to this study as prescriptions for a few patients could influence the results.

In Lemvig municipality the prescription of antipsychotics is substantially under the county average. Part of the explanation may be that there is only one major psychiatric institution in the area. There may therefore be a departure from the municipality by users of antipsychotics to regions having multiple psychiatric facilities. Part of the slight increase in prescription of antipsychotics noted in the municipality during the intervention may be attributed to patients with psychiatric diseases for whom, upon reduction of their prescriptions of benzodiazepine and cyclopyrrolone, it is discovered that they could be more appropriately treated with antipsychotics.

In accordance with the present study, the consumption of antidepressants during the intervention showed no significant increase (Jørgensen, 2010).

This study does not address the quality of treatment with antipsychotics. It is also not possible to infer from the results whether an under- or over-treatment took place. In addition, the study provides no information about changes in prescrip-

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**Fig. 1.** The total volume of prescribed antipsychotics in Ringkøbing County. The columns indicate average daily defined doses (DDD) per quarter per thousand registered patients for the year indicated. Errors bars indicate least significant difference \( (p = 0.05) \) calculated using Analysis of Variance followed by the Student–Newman–Keuls post-ANOVA test.

**Fig. 2.** Change in the prescription of antipsychotics for individual practices over a 1½ year period. On the x-axis, practices are identified by a double-digit code, with “Total” indicating the total average change. (A) Changes in the daily defined doses (DDD) per quarter per thousand registered patients. The first column indicates the average prescription rate in the four quarters prior to the intervention (“Before”), while the second column indicates the prescription rate in the sixth quarter following the start of the intervention (“After”). (B) The percent change in prescriptions of antipsychotics for individual practices.
tions to individual users or about changes in the numbers of users. This study answers only the question of whether the total prescribed amount of antipsychotics increased as a result of the restrictive attitude towards the prescription of benzodiazepines and cyclopyrrolones.

The intervention was implemented on a voluntary basis in Lemvig. The patient was at all times the focal point of the intervention, and changes in prescriptions were the result of months of consultations and were usually based on consensus.

The overall result shows that a reduction in the prescription of benzodiazepines and cyclopyrrolones does not necessarily lead to a concomitant, uncontrollable increase in the prescription of psychotherapeutic drugs. In the individual practices involved in the intervention, a considerable variation in changes in the prescription of antipsychotics could be observed. Accordingly, the education of practitioners in the prescription of alternative psychotherapeutic drugs is to be recommended in future interventions of a similar nature.

4. Conclusion

A reduction in the prescription of benzodiazepine and cyclopyrrolone does not necessarily lead to a concomitant, uncontrollable increase in the prescription of antipsychotic drugs. The overall increase in the prescription of antipsychotics during the intervention described here was not more than 3.1% of the reduction in prescriptions of benzodiazepines and cyclopyrrolone measured in DDD.

It is therefore recommended that the few simple rules presented here are followed when prescribing benzodiazepines and cyclopyrrolones.

Role of the funding source

The author has received honoraria from public funding for the further education of practitioners for lecturing on drug reduction in clinical practice.

Conflict of interest

The author is a part time employee of the Medicine Team, Central Denmark Region, and has received honoraria from public funding for the further education of practitioners for lecturing on drug reduction in clinical practice, as well as funding within the constraints of the Danish Medicines Agency from the pharmaceutical industry for three lectures on drug reduction in clinical practice.

Acknowledgements

Thanks are extended to practitioners in Lemvig for their cooperation, as well as their willingness to be the first to implement the new rules in a larger region.

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Fig. 3. Change in the total prescription of antipsychotics issued by twelve Danish practices, during six quarters following the start of the intervention. The first column (“Total”) indicates the total change in prescriptions. On the x-axis antipsychotic groups are identified as defined in Table 1.


