

# Concomitant use of two or more antipsychotic drugs is common in Sweden

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## Abstract

**Objectives:** To assess the prevalence of concomitant use of two or more antipsychotic drugs and other psychotropic drugs in the Swedish population.

**Methods:** Data for this observational cohort study were collected from the Swedish Prescribed Drug Register including all dispensed drugs to the entire Swedish population (9.4 million inhabitants). We identified all individuals with at least one dispensed prescription of antipsychotic drug during January to June 2008. After 12 months, a second exposure period was chosen. Individuals who were dispensed two or more antipsychotic drugs in both periods were considered long-time users of antipsychotic polypharmacy.

**Results:** In 2008, 1.5% of the Swedish population was dispensed antipsychotic drugs, the majority (75%) using only one antipsychotic drug. Out of individuals who were dispensed 2 or more antipsychotic drugs during the first period, 62% also was also dispensed at least 2 antipsychotic drugs during the second period. A total of 665 different unique combinations were used in 2008. Individuals prescribed two or more antipsychotic drugs during both periods were more often dispensed anxiolytics and sedatives than those who were dispensed only one antipsychotic drug. Elderly were dispensed antipsychotic drugs much more often than younger persons.

**Conclusions:** In Sweden, 25% of patients dispensed antipsychotic drugs receive a combination of two or more antipsychotic drugs. Individuals who are dispensed antipsychotic polypharmacy are more often dispensed anxiolytics and sedatives than those prescribed only one antipsychotic drug. Long-term observational studies are needed to assess the efficacy and safety of such combinations.

**Keywords:** antipsychotic agents, drug polytherapy, drug utilization, polypharmacy, psychotic disorders, schizophrenia

## Introduction

Most psychiatrists come across patients with a combination of prescription drugs that challenge all guidelines and scientific evidence. Since 50 years, antipsychotic drugs are the pharmacological treatment of choice for most patients with schizophrenia and other psychotic disorders. The vast majority of clinical trials are made with monotherapy. Due to the severity of schizophrenia, many patients do not recover with one antipsychotic drug and, consequently, it is common practice to try different combinations of drugs. There are, however, few studies analyzing the benefit or risk of combination treatment with  $\geq 2$

antipsychotic drugs [Schumacher *et al.* 2003; Tapp *et al.* 2003; Ganguly *et al.* 2004; Broekema *et al.* 2007; Kreyenbuhl *et al.* 2007a, 2007b; Megna *et al.* 2007; Lee and Walker, 2008; Pandurangi and Dalkilic, 2008; Tranulis *et al.* 2008]. Since antipsychotic drugs may cause severe side effects such as cognitive and emotional blunting, acute and chronic extrapyramidal side effects, torsade de pointes, weight gain and metabolic syndrome [Jeste and Caligiuri, 1993; Raschi *et al.* 2013], these drugs should be used with utmost care and only when really needed. Despite severe side effects and high treatment costs and the lack of evidence, there is a widespread use of

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antipsychotic drugs as sedatives–hypnotics even in the absence of a psychotic or bipolar disorder [Schmidt and Fastborn, 2000]. Several of the newest generation antipsychotic agents are also used as long-term mood stabilizers, either alone or in combination with lithium, and as treatment for manic episodes [Sanches *et al.* 2010; De Fazio *et al.* 2010]. An agitated in-patient may be prescribed several psychotropic drugs by different doctors resulting in strange combinations. The regular physician may miss that on-call doctors have added new drugs. It is always hard to assess the effect of a specific drug in patients receiving many different drugs.

Many elderly patients with dementia are prescribed antipsychotic drugs rather as an unspecific sedative than as an antipsychotic agent. Elderly are particularly sensitive to antipsychotic drugs, and get more severe acute and chronic extrapyramidal side effects [Jeste, 2000]. The positive effect is questionable and mortality increases [US Food and Drug Administration, 2008], although it has recently been proposed that it is the severity of the disease rather than the antipsychotic drug that causes the increased mortality in Alzheimer patients receiving antipsychotic drugs [Lopez *et al.* 2013].

The establishment of the Swedish Prescribed Drug Register in 2005 created new opportunities for studies of polypharmacy [Haider *et al.* 2009; Lesen *et al.* 2009; Wettermark *et al.* 2007]. This register includes all dispensed drugs to the entire Swedish population (9.4 million inhabitants). Each year approximately 90 million prescriptions are recorded for more than 6 million individuals (two-thirds of the Swedish population use prescription drugs). Consequently, the register represents one of the largest population-based pharmacoepidemiological databases in the world.

The aim of this study was to assess the prevalence of the simultaneous use of two or more antipsychotic drugs in the Swedish population.

### Material and methods

This was an observational cohort study based on data on dispensed prescriptions of antipsychotic drugs to the entire Swedish population collected from the Swedish Prescribed Drug Register [Wettermark *et al.* 2007]. The register contains

patient identity data on substance, brand name, formulation and package as well as date of prescribing and dispensing. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The register is managed by the National Board of Health and Welfare. Over-the-counter (OTC) medications and drugs used in hospitals are not included. Most nursing home patients get their drugs dispensed on prescriptions or multidose dispensing, and are thus included in the register. Antipsychotic drugs (ATC N05A) except lithium registered in Sweden in 2008 are listed in Table 1 along with the number of dispensed defined daily doses (DDDs). Some nonregistered antipsychotic drugs prescribed on special permission from the regulatory agency were also included.

The period prevalence of antipsychotic drug use was assessed as the proportion of subjects in the Swedish population that were dispensed antipsychotic drugs during 2008 and 2009, respectively. Due to its unique position as a mood stabilizer in bipolar disorders and lack of evidence for treatment of schizophrenia, lithium was excluded from the analysis. All antipsychotic drugs except lithium are referred to as APD in this paper.

The incidence of new APD users was assessed by identifying individuals purchasing an antipsychotic drug for the first time after a 1 year run-in period without any dispensed antipsychotic drugs. To investigate the long-term use of multiple antipsychotic drugs, we identified all persons with at least 1 dispensed prescription APD during a period of 6 months (January to June 2008, exposure window 1). Among these we identified individuals purchasing  $\geq 2$  APDs during the period. To minimize the number of patients on cross-titration, a second exposure window was chosen after a period of 12 months (January to June 2009, exposure window 2). Patients who were still dispensed  $\geq 2$  APDs were identified and considered long-time users of antipsychotic polypharmacotherapy [Fincke *et al.* 2005]. The length of the windows (6 months) and the antipsychotic free run-in period (1 year) to determine incidence were selected because the Swedish reimbursement system allows patients to be dispensed drugs for a period of 3 months at the time to receive full reimbursement. For long-term users of  $\geq 2$  APDs, concomitant dispensing of adjuvant psychotropic medication was also studied for opiates (N02A), anxiolytics (N05B), sedatives

**Table 1.** Antipsychotic drugs dispensed in ambulatory care in Sweden during 2008.

ATC code and substance name	No. of DDDs	ATC code and substance name	No. of DDDs
N05AH03 Olanzapin	6,461,443	N05AD03 Melperon	123,364
N05AN01 Litium	5,323,841	N05AF03 Klorprotixen	116,236
N05AX08 Risperidon	3,709,272	N05AB01 Dixyrazin	36,876
N05AF05 Zuklopentixol	2,074,121	N05AC02 Tioridazin	36,558
N05AD01 Haloperidol	1,841,969	N05AG02 Pimozid	35,842
N05AH04 Quetiapin	1,800,467	N05AB04 Proklorperazin	29,036
N05AH02 Klozapin	1,783,062	N05AA01 Klorpromazin	15,926
N05AB03 Perfenazin	1,491,791	N05AE03 Sertindol	9492
N05AX12 Aripiprazol	1,270,095	N05AX13 Paliperidon	8820
N05AF01 Flupentixol	755,546	N05AL01 Sulpirid	6685
N05AA02 Levomepromazin	696,561	N05AL03 Tiaprid	1048
N05AE04 Ziprasidon	636,867	N05AC01 Periciazin	938
N05AB02 Flufenazin	213,000	N05AD05 Pipamperon	116

ATC, Anatomical Therapeutic Chemical; DDD, defined daily dose.

(N05C), antidepressants (N06A) and antidementia drugs (N06D). Patients who died during the observation period were identified using the Swedish cause-of-death register [Furu *et al.* 2010].

### Ethical considerations

All analyses were undertaken by the Swedish National Board of Health and Welfare, which is a government agency that, in accordance with Swedish law, can use population-based registers to follow and analyse health and social conditions among the general population. All data were made anonymous for the research team with no possibility to identify any individual patient.

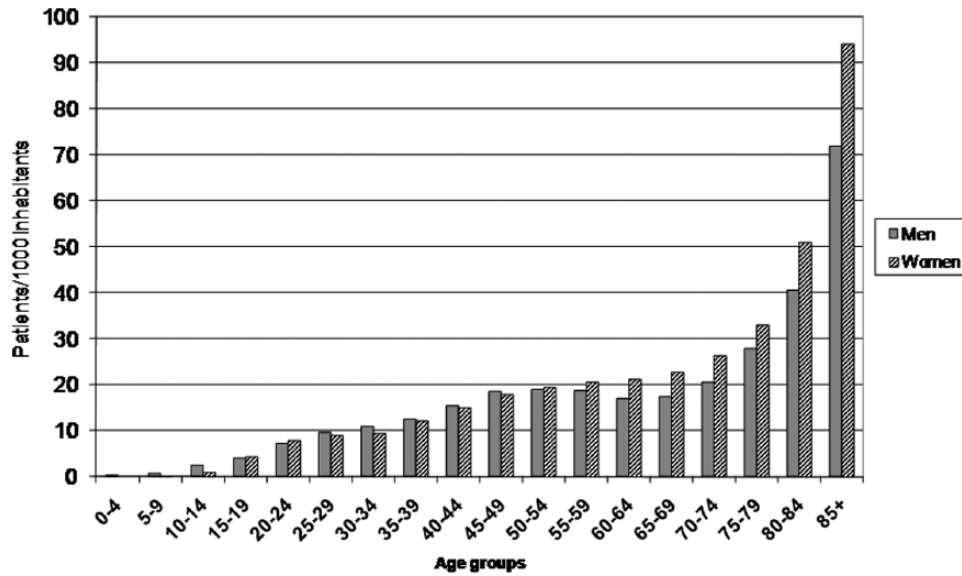
### Results

In 2008, 132,000 persons, corresponding to 1.5% of the Swedish population were dispensed APDs. In addition, 11,000 persons were dispensed lithium. Figure 1 shows the number of patients dispensed APDs per 1000 inhabitants in Sweden during 2008 split by age and sex. The utilization of antipsychotic drugs was scarce among children and increased from puberty to about 45 years of age. Then it remained stable until about 65 years of age, but tripled in the group aged 85 years and older. Men used antipsychotic drugs more often than women until about 50 years of age. Thereafter women used more antipsychotic drugs than men (Figure 1).

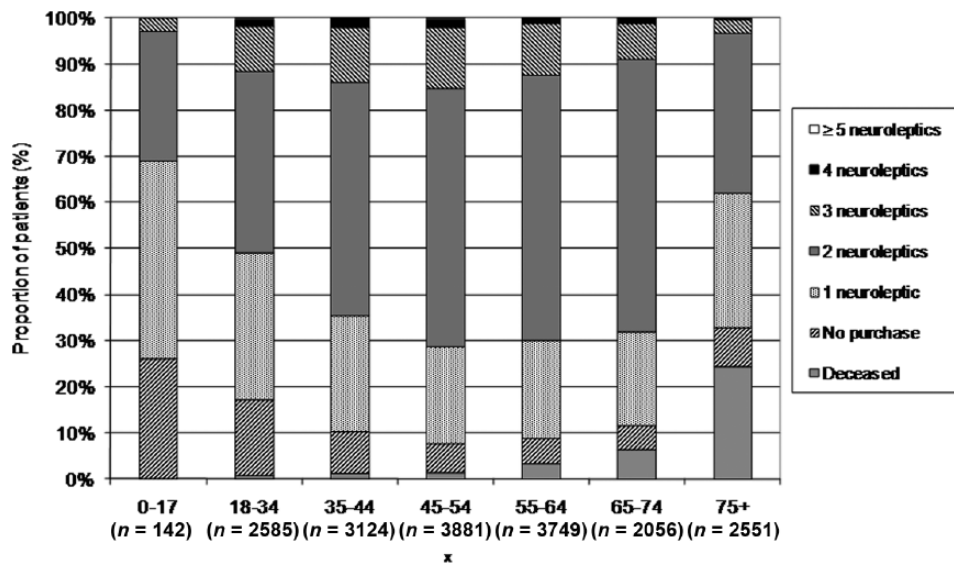
During the year, a total of 34,100 patients were initiated on APD treatment. This corresponds to an incidence rate of 3.7/1000 person-years. For persons aged 75+, the incidence was 15.6/1000 person-years. The overall use of APDs in Sweden decreased by 3% in 2009 compared with 2008. The decrease was most pronounced among patients over 80 years of age (18%). Correspondingly, in 2009 the incidence rate had decreased to 3.5/1000 person-years. For persons aged 75+, the incidence decreased by 18% to 12.7/1000 person-years.

The total number of individuals purchasing at least one APD during both exposure windows was 80,576 (44,074 females and 36,502 males). Among these, 60,597 individuals (75%) were dispensed only one APD during both exposure windows.

Of the 18,088 individuals who were dispensed  $\geq 2$  APDs during exposure window 1, 988 (5%) died before exposure window 2. In addition, 1513 persons (8%) did not purchase any APDs during the second period. A total of 11,142 (62%) were dispensed at least 2 APDs during both windows (Table 1, Figure 2). In the youngest group (0–17 years of age), about 25% were not dispensed any APDs during the second period and about 45% were dispensed a single APD. In those aged 18–34, about 17% were not dispensed any APD, but 30% were dispensed 1 APD and 40% two APDs.



**Figure 1.** Utilization of antipsychotic drugs in Sweden during 2008 by age and sex.



**Figure 2.** Individuals dispensed two or more antipsychotic drugs during January to June 2008, and the number of antipsychotic drugs they were dispensed during January to June 2009, by age groups.

In the group aged 45–74, about 50% were dispensed 2 APDs and 70%  $\geq 2$  APDs.

*Different combinations of substances*

Of the 8370 individuals who were dispensed 2 APDs during both time windows, 800 were dispensed the same combination during both periods whereas 7570 had a different combination. For the individuals with combinations of 3

APDs, 132 of 1022 had the same combination during both periods. Among individuals who were dispensed 4 APDs during both time windows, 13 of 85 had the same combination of drugs. The individuals who were dispensed  $\geq 5$  APDs are not reported due to small numbers (Table 2).

A total of 665 different unique substance combinations were used in 2008. The most commonly

**Table 2.** Individuals dispensed two or more antipsychotic drugs during January to June 2008, and the number of antipsychotic drugs they were dispensed during January to June 2009.

No. of substances in 2008	Deceased ≤30 June 2009	2009					
		No purchase	1 substance	2 substances	3 substances	4 substances	≥5 substances
<b>2 (n = 15,339)</b>	882 [5.8%]	1337 [8.7%]	3984 [26.0%]	8370 [54.6%]	705 [4.6%]	57 [0.4%]	4 (<0.1%)
<b>3 (n = 2404)</b>	97 [4.0%]	156 [6.5%]	410 [17.1%]	620 [25.8%]	1022 [42.5%]	90 [3.7%]	9 [0.4%]
<b>4 (n = 313)</b>	9 [2.9%]	19 [6.1%]	43 [13.7%]	82 [26.2%]	69 [22.0%]	85 [27.2%]	6 [1.9%]
<b>≥5 (n = 32)</b>	0	1 (<0.1%)	8 [25.0%]	5 [15.6%]	6 [18.8%]	4 [12.5%]	8 [25.0%]
<b>Total (n = 18,088)</b>	988	1513	4445	9077	1802	236	27

**Table 3.** Most commonly dispensed combinations of antipsychotic drugs N05A January to June 2008. \*

Combination of two substances	n	Combination of three substances	n
levomepromazine + risperidone	1119	Levomepromazin + zuklopentixol + olanzapin	118
levomepromazine + olanzapine	961	Levomepromazin + haloperidol + olanzapine	106
olanzapine + risperidone	788	Levomepromazin + perphenazine + olanzapine	84
levomepromazine + haloperidol	780	Levomepromazin + olanzapin + risperidone	83
haloperidol + risperidone	656	Levomepromazin + zuklopentixol + risperidone	68

\*Lithium is excluded.

dispensed combination was levomepromazine + risperidone (Table 3).

*Concomitant use of other psychotropic drugs*

Out of the 11,142 individuals with ≥2 APDs both during the first and the second time window, a total of 5058 (45%) were dispensed anxiolytics (N05B), 5468 (49%) were dispensed sedatives (N05C), 4683 (42%) were dispensed antidepressants (N06A), 1060 (10%) were dispensed opiates (N02A) and 78 (1%) were dispensed antedementia drugs during the second time window. The corresponding figures for the 60,597 patients only purchasing 1 APD in both periods were 35% (anxiolytics), 40% (sedatives), 47% (antidepressants), 15% (opiates) and 4% (antedementia drugs), respectively.

**Discussion**

To our surprise, there were a total of 665 unique combinations of APDs. However, the majority of patients (75%) were dispensed only 1 APD. Among those who were prescribed >1 APD at baseline, only about 10% had the same combination of

APDs the next year. Since many patients with schizophrenia and other psychoses do not recover in spite of following guidelines, it is reasonable to try other treatment strategies under careful observation of the patients. Without clinical data, we had no possibility of judging if concomitant use of more than one APD was good or bad for the individual patient. In addition, those taking two APD during both periods were more often taking anxiolytics and sedatives than those taking only one APD. It is a fair guess that those patients are very sick and difficult to treat from many points of view. On the contrary, individuals taking one APD were more often taking opiates, suggesting that some patients in palliative care were included in this group. Combinations of an APD and opioids are partly used for the relief of pain and nausea.

Levomepromazine has been available in Sweden since 1959 and has strong anticholinergic and sedative properties. It was present in the two most common combinations of two antipsychotics, and in the three most common combinations of three antipsychotics. It is likely that levomepromazine is used widely for sleep and sedation due to its sedative properties.

Schizophrenia usually starts during teens and early adulthood, and strikes men more severely than women [Hafner, 2003]. There is a second peak of onset for women about the time of menopause. Our finding of a slightly higher consumption of APDs in men until about 50 years of age and higher in women thereafter is in accordance with this. The use of APDs was highest among the oldest patients, although schizophrenia is rare in this group due to increased mortality. Psychotic symptoms do occur in the elderly due to delirium, degenerative changes in the brain, dementia or as a part of depression. If an elderly person presents with psychotic symptom, a careful workup should be started to determine the underlying cause. APDs should be used with great caution in the elderly, which is not always the case. In nursing homes, the access to doctors is limited and APDs may be used as sedatives, also in the absence of a proper indication. The elderly are more sensitive to extrapyramidal and anticholinergic effects than young people, and have more somatic disorders and thus more other drugs.

In 2005, there were international alarm reports about the increased risk for death for patients with dementia using modern generation antipsychotics (US Food and Drug Administration, 2008).

The Swedish drug regulatory agency, the Medical Products Agency, which released its guidelines on Behavioural and Psychological Problems in Dementia (BPSD) in October 2008, strongly recommended other treatment strategies than drugs for this group. We believe that the new guidelines may have contributed to the decrease in the use of APDs for this group in Sweden.

In our study, mortality actually decreased with the number of APDs dispensed at baseline, contrary to what one would expect. The reason for this is unknown, but it may well be that this group of patients with extensive pharmacological APD treatment is carefully monitored by the healthcare profession. Alternatively, a combination therapy may actually be beneficial.

This study was based on the Swedish Prescribed Drug Register, which is one of the largest population-based databases in the world. We used data on dispensed drugs to determine concomitant use. To assess polypharmacy using registers is a challenge since we only have information on dispensed drugs and not on the actual use of these

drugs. However, the agreement between dispensed prescriptions and self-reported data in a cohort of elderly residents in Finland was shown to be almost perfect or substantial for all antipsychotic drugs. The authors emphasized the need to select a time window in the register with caution since the sensitivity decreased with shorter time periods [Haukka *et al.* 2007; Rikala *et al.* 2010].

It is also important to recognize that there are certain limitations concerning the methodology. There is no gold standard on how to study polypharmacy in registers. We used a modified version of the method proposed by Fincke and colleagues [Fincke *et al.* 2005]. The reason for using a 12 month gap instead of a 6 month gap was an attempt to control for cross-titration at the beginning of therapy and to assess long-term use of  $\geq 2$  APDs. We have no information on diagnosis for the individuals in this study and a previous report estimated that approximately 25% of antipsychotics were prescribed to individuals without psychotic disease [SBU, 1997].

Despite the limitations, this study covering the total APDs dispensed in Sweden has clarified the extent of concomitant use of more than one APD. There is no way to assess the efficacy and safety of all those combinations in randomized clinical trials. Researchers must consider other ways of doing systematic research on this patient group, such as postmarketing surveillance studying using observational data from healthcare quality registers. This has proven helpful for other categories of patients and drugs [Askling *et al.* 2006; Kobelt *et al.* 2008]. A second opinion and re-evaluation of diagnosis, social situation and compliance, medication review by a clinical pharmacologist, a survey of nonprescription drugs that may interfere with APDs, pharmacogenetic assessment and blood level analysis of drugs should be offered systematically to therapy-resistant patients. This can be implemented by educational activities for physicians by, for example, the local Drug Therapeutic Committee that has the competence and network for this.

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### Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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