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Prevalence of Therapeutic Drug Monitoring for Antidepressants and Antipsychotics in Stockholm, Sweden: A Longitudinal Analysis

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Background: Although therapeutic drug monitoring (TDM) is considered an underused tool in psychiatric care, the prevalence of TDM is largely unknown. The aim of this study was to analyze the prevalence of TDM for antidepressants and antipsychotics during 2006–2013.

Methods: The study population consisted of individuals ≥5 years of age residing in Stockholm County. The prevalence of TDM for each study year was calculated with the number of individuals in whom TDM had been performed as nominator (extracted from the TDM database at Karolinska University Laboratory) and the number of treated individuals as denominator (extracted from the Swedish Prescribed Drug Register). All data were obtained at the third and the fifth level of the anatomical therapeutic chemical classification system (pharmacological subgroup and chemical substance, respectively). The prevalence of TDM was compared between substances according to the level of TDM recommendation by guidelines.

Results: For antidepressants, the prevalence of TDM decreased from 0.48% (95% confidence interval, 0.45%–0.52%) in 2006 to 0.36% (0.33%–0.39%) in 2013 (among 133,275 and 162,998 treated individuals, respectively). For antipsychotics, the prevalence of TDM increased from 2.3% (2.2%–2.5%) to 4.1% (3.9%–4.3%) (31,463 and 32,534 treated individuals). For both drug groups, TDM was more common in men than in women. The most frequently analyzed drugs were clozapine, perphenazine, zuclopenthixol, nortriptyline, and flupentixol. Although not reaching statistical significance, the TDM prevalence was greater for substances strongly recommended for TDM than for substances with a lower level of recommendation, median (interquartile range): 5.6% (2.8%–22%) versus 1.1% (0.2%–2.2%), $P = 0.063$.

Conclusions: The prevalence of TDM is generally low, more frequent, and increasing for antipsychotics, and more frequent for men and substances where TDM is strongly recommended.

Key Words: antidepressants, antipsychotics, prevalence, therapeutic drug monitoring

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INTRODUCTION

Therapeutic drug monitoring (TDM) is a tool to guide clinicians regarding the drug treatment of individual patients, constituting an approach to *personalized medicine*. Measurements of drug concentrations can be useful for example in cases of uncertain drug adherence, adverse drug reactions, therapeutic nonresponse, or pharmacokinetic drug–drug interactions.[1] TDM is based on an assumption of a relationship between the plasma concentration of the drug and its clinical effect. Thus, measuring drug concentrations can help the clinician to optimize the dosing of medicines to achieve the wanted (therapeutic) effects and to reduce the risk of unwanted (adverse) effects.

In psychiatry, plasma concentrations of several drugs have been related to receptor occupancy.[2] These findings suggest that TDM may add valuable information in the pharmacological management of psychiatric disease and, recently, consensus guidelines on TDM in psychiatry have been updated.[3] According to available evidence, these guidelines categorize TDM for the individual substances as "Strongly recommended," "Recommended," "Useful," or "Potentially useful." Indeed, TDM may be particularly appropriate in psychiatry for several reasons. First, the full clinical effects can often be expected only after several weeks of treatment. Therefore, optimal dosing may be hard to achieve within a reasonable time frame. Second, the effects cannot be as easily monitored as can, for example, the blood pressure in hypertension. In addition, many adverse effects are concentration-dependent, and TDM can, for instance, be used to avoid extrapyramidal side effects of antipsychotics.

TDM is considered an underused tool in psychiatry.[4,5] However, as far as we are aware, data on the prevalence of TDM for antidepressants and antipsychotics are lacking. The aim of this study was to determine the prevalence of TDM for these drugs in a large patient sample, with special focus on time trends and variations attributable to patient sex and age as well as the level of recommendation for TDM for specific drugs.

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MATERIALS AND METHODS

Setting and Participants

To determine the prevalence of TDM for antidepressants and antipsychotics, we merged data from 2 sources: the Swedish Prescribed Drug Register and the TDM database at the TDM Laboratory, Department of Clinical Pharmacology, Karolinska University Hospital. We included individuals residing in the Stockholm County and extracted yearly data during an 8-year period (2006–2013). Individuals <5 years of age were excluded because TDM measurements in small children often concern drugs transferred from the mother in utero or through the breast milk.

The TDM laboratory currently offers plasma concentration analyses for 10 of 17 antidepressants and 10 of 19 antipsychotics available for prescription in Sweden. As these antidepressants and antipsychotics account for the treatment of approximately 90% and 80% of the individuals in each drug class,[6] the available TDM analyses covers all commonly prescribed drugs. As compared with some specialized pharmacological laboratories, for example in Norway,[7] the coverage of our TDM analyses may be lower. However, compared with other countries, for example China,[8] our coverage is substantially greater.

Typically, the samples are analyzed within a week after arriving at the laboratory, at a price of 75–90 USD excluding discounts. The reporting of the results includes a clinical interpretation based on published evidence, often in accordance with the guidelines issued by the TDM expert group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie.[3] In addition, most measurements of antidepressants are accompanied by a graphical presentation where the result is compared with dose-concentration data from previously analyzed samples.[1]

Data Extraction

From the publicly available Website of the Swedish Prescribed Drug Register,[6] we extracted aggregated data on the number of individuals who purchased an antidepressant drug (N06A according to the third level of the anatomical therapeutic chemical classification system)[9] or an antipsychotic drug (N05A). Data were extracted separately for men and women, as well as according to age group (5–9 years, 10–14 years, etc). We also extracted data on the chemical substance level, that is, the fifth level of the anatomical therapeutic chemical system. The number of individuals who had purchased a drug was used as an approximation of the number of treated individuals.

From the TDM database, we extracted yearly data on the number of individuals and the number of measurements, aggregated according to sex and age group. We extracted data for antidepressants and antipsychotics as drug groups, and data for individual drugs within these groups. To our knowledge, the TDM laboratory is the only laboratory in Stockholm County that analyzes plasma concentrations of antidepressants and antipsychotics. Hence, the number of Stockholm residents registered in the TDM database should be a valid approximation of the total number of patients where TDM was used to guide therapy.

Data Analysis

Data handling and analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 17.0, Armonk, NY). Prevalence of TDM including 95% confidence intervals for drug groups and for individual drugs was calculated with the number of individuals with TDM as nominator and the number of treated individuals as denominator. Mann–Whitney *U* test was used to compare the prevalence of TDM between drugs with and without the highest level of recommendation for TDM by guidelines.[3]

Ethical Considerations

This study comprised aggregated data only. Therefore, the Ethical Review Act was not applicable, and no ethical approval was obtained.

RESULTS

A total of 24,471 TDM measurements performed between 2006 and 2013 were included in the analysis. In all, 28 TDM measurements could not be included because information on sex or age was missing. An additional 109 TDM measurements were excluded because of patients being younger than 5 years of age.

Between 2006 and 2013, the number of individuals prescribed an antidepressant increased from 133,275 to 162,998 (Table 1). TDM was performed in 0.48% (95% confidence

TABLE 1. Number of Individuals on Treatment and With TDM Measurements For Antidepressants and Antipsychotics During the Studied 8-Year Period

	Antidepressants		Antipsychotics	
Year	Treated Individuals, n	Individuals With TDM, n (%)	Treated Individuals, n	Individuals With TDM, n (%)
2006	133,275	641 (0.48)	31,463	729 (2.3)
2007	136,755	660 (0.48)	29,164	939 (3.2)
2008	138,362	685 (0.50)	28,939	1037 (3.6)
2009	139,854	545 (0.39)	28,951	1118 (3.9)
2010	143,977	568 (0.39)	30,104	1258 (4.2)
2011	150,025	618 (0.41)	30,779	1378 (4.5)
2012	155,740	584 (0.38)	31,267	1404 (4.5)
2013	162,998	580 (0.36)	32,534	1338 (4.1)

interval, 0.45%–0.52%) and 0.36% (0.33%–0.39%) of the patients, respectively. Throughout the period, the prevalence of TDM was greater in men than in women (Fig. 1). In 2013, 237 of 54,800 men and 343 of 108,200 women with any antidepressant had their drug plasma concentration measured at least once: 0.43% (0.38%–0.49%) versus 0.32% (0.29%–0.35%).

The number of individuals prescribed an antipsychotic was 31,463 in 2006 and 32,534 in 2013 (Table 1). TDM was performed in 2.3% (2.2%–2.5%) and 4.1% (3.9%–4.3%) of patients, respectively. As for antidepressants, the prevalence of TDM for antipsychotics was greater in men than in women (Fig. 1). In 2013, 751 of 14,673 men and 586 of 17,861 women with any antipsychotic had ≥1 TDM measurement: 5.1% (4.8%–5.5%) versus 3.3% (3.0%–3.6%).

As shown in Figure 2, TDM was more frequently used to guide treatment with antidepressants and antipsychotics in young and middle-aged adults compared with children and older patients.

The most frequently analyzed drugs were clozapine (18%–30% of treated individuals each year; n = 918 in 2006 and n = 1084 in 2013), perphenazine (6.9%–22%; n = 1867 and n = 836), zuclopenthixol (7.4%–11%; n = 1881 and n = 1865), nortriptyline (6.2%–19%; n = 377 and n = 405), and flupentixol (5.4%–9.1%; n = 2531 and n = 2046). The longitudinal prevalence of TDM for substances where TDM had been performed is illustrated in Figure 3.

In 2013, although not reaching statistical significance, the prevalence of TDM was higher for drugs where guidelines strongly recommended TDM (amitriptyline, nortriptyline, clomipramine, haloperidol, clozapine, olanzapine, and perphenazine) than for substances with a lower level of recommendation (citalopram, escitalopram, fluoxetine, sertraline, mirtazapine, venlafaxine, aripiprazole, flupentixol, paliperidone, quetiapine, risperidone, paroxetine, and zuclopenthixol), median percentage (interquartile range), 5.6 (2.8–22) versus 1.1 (0.2–2.2), $P = 0.063$.

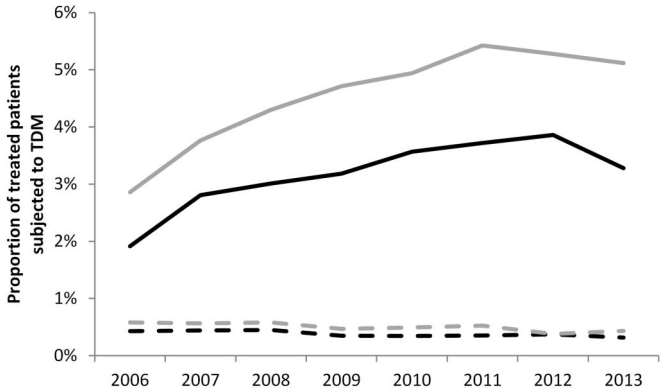

FIGURE 1. Longitudinal prevalence of TDM for antidepressants (dashed lines) and antipsychotics (solid lines). Women (black lines) and men (gray lines) are presented separately.

DISCUSSION

Main Findings

Each year, TDM is performed in less than 1 in 200 patients on antidepressants and less than 1 in 20 patients on antipsychotics. Thus, TDM is a tool that clinicians seldom take advantage of, particularly in the management of treatment with antidepressants. Encouragingly, TDM tends to be most frequently used for drugs with the strongest evidence for this tool.

The prevalence of TDM is increasing for antipsychotics, and while the number of individuals on antipsychotics has been relatively stable, the use of TDM has almost doubled. For antidepressants, however, the number of individuals using these drugs has increased steadily, while the use of TDM has remained stable or even decreased. For both drug groups, TDM is more often used to guide treatment of male than female patients.

Strengths and Weaknesses

The most important strength of this study is the population-based approach. Indeed, the Swedish Prescribed Drug Register[10] covers all individuals within the geographic area. Furthermore, as far as we are aware, no laboratory in the county, other than the TDM Laboratory in the Department of Clinical Pharmacology, Karolinska University Hospital, performs TDM analyses for either antidepressants or antipsychotics. Thus, all individuals who purchased an antidepressant or an antipsychotic within the study period were included, as were all TDM measurements for these drugs. Consequently, the prevalence figures are likely to reflect TDM in clinical practice. Another strength is that the data are substantial and span over several years, allowing analyses of longitudinal trends and differences attributable to patient sex and level of evidence for usefulness of TDM.

A weakness of the study is that the analyzed data were aggregated. Thus, the individual years of the study period cannot be combined to achieve overall figures on the prevalence of TDM over the full 8-year period. In addition, the Swedish Prescribed Drug Register contains only drugs, which are both prescribed and dispensed. The prevalence figures may therefore overestimate the use of TDM. Indeed, one reason to use TDM is suspicion of noncompliance, and noncompliant patients would not necessarily have purchased the drug in question and may therefore not be included in the denominator. Nevertheless, we consider this study as an appropriate first approach to examine the prevalence of TDM in clinical practice, important information that has hitherto been lacking in the scientific literature.

Comparison With Previous Research

The low prevalence of TDM found in this study, although increasing for antipsychotics, supports previous statements of underuse of TDM in psychiatry.[4,5] Indeed, general practitioners and psychiatrists have reported that they seldom use TDM.[11] However, because the optimal frequency of TDM in clinical practice has not been evaluated, the extent of underuse cannot be determined.

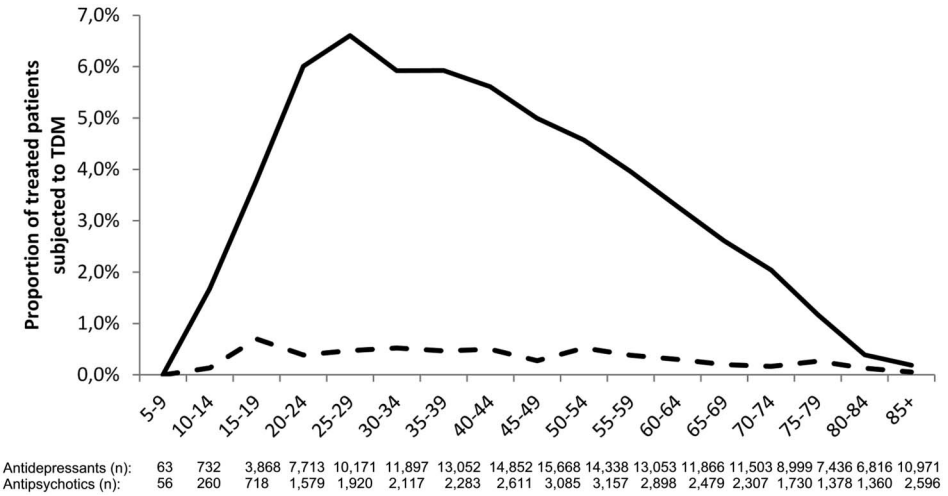

FIGURE 2. Prevalence of TDM and number of treated individuals in 2013 for antidepressants (dashed lines) and antipsychotics (solid lines) according to age group (years on the *x*-axis).

The proportion of patients on antidepressants for whom TDM was performed decreased during the study period. This may sound discouraging, because TDM has been shown to be cost-effective for drugs within this drug group.[12,13] One explanation for the decrease may be that, over the years, pharmacotherapeutic traditions and recommendations may have shifted to substances where TDM is less common. In fact, new antidepressant products have emerged in the latest

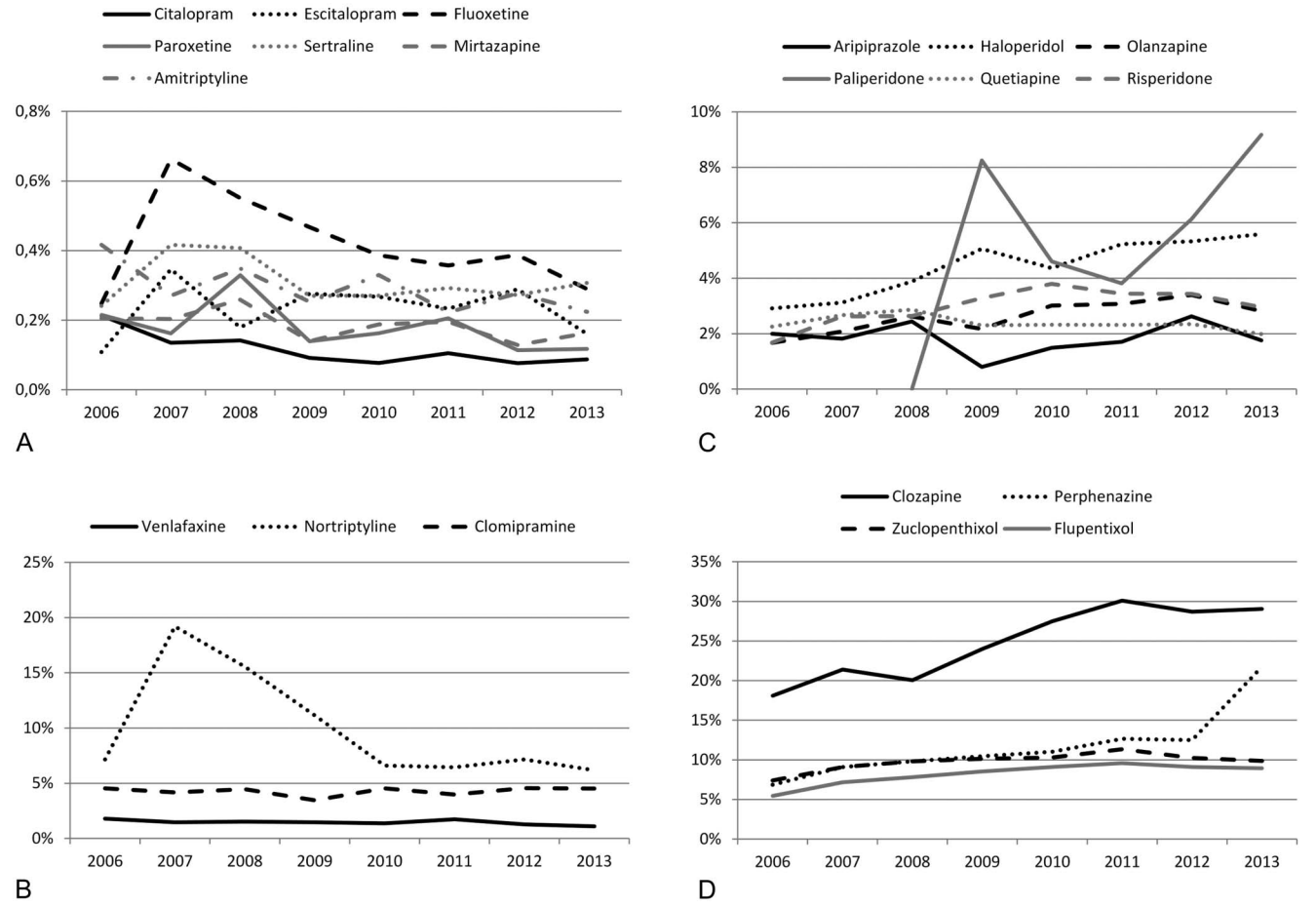

FIGURE 3. Longitudinal prevalence of TDM. The *y*-axis displays the proportion of treated patients subjected to TDM. In (A) and (B), antidepressants with a prevalence <1% and >1%, respectively, are presented. In (C) and (D), antipsychotics with a prevalence steadily <5% and >5%, respectively, are presented.

years, e.g. bupropione and agomelatine, and TDM for these is yet to be established in our laboratory.

Underlying reasons for the low prevalence of TDM in psychiatry need to be speculated on. Lack of knowledge among prescribers on when and how to use this service may constitute one reason. Indeed, 1 in 3 psychiatrists has been reported not to consider TDM of value for clinical outcome.[14] Thus, education of physicians may be a key factor to increase the use of TDM in psychiatry. Another contributing factor for the low prevalence of TDM may be a limited budget for laboratory services.

Interestingly, the prevalence of TDM was about 5 times higher for drugs where TDM is strongly recommended compared with drugs with a lower level of recommendation.[3] In fact, the 3 substances with the top TDM prevalence figures during the study period are all strongly recommended for TDM. During the years studied, TDM was performed in up to 1 in 3 patients on clozapine and in 1 in 5 patients on perphenazine or nortriptyline. The finding of a high prevalence of TDM for clozapine may not be surprising as questionnaire studies show that more than 80% of London psychiatrists use TDM routinely for this drug,[14] and in Italy, clozapine TDM is considered as obligatory to that of blood cell counting.[15] Furthermore, TDM for clozapine has been suggested to reduce the risk of toxicity.[16] Regarding the conspicuous peak in the proportion of individuals with TDM for nortriptyline in 2007, we do not have any explanation. Indeed, the number of treated individuals was not particularly low in that year (n = 349) as compared with the other years (range, 333–419). Regarding the fluctuating prevalence of TDM for paliperidone, this may be explained by the small number of patients treated with this drug when it was first marketed (n = 21 in 2008 and n = 512 in 2013).

Somewhat surprisingly, TDM was more frequently undertaken in men than in women, both for antidepressants and for antipsychotics. Underlying factors can only be speculated on. For example, potential sex differences in pharmacokinetics, pharmacodynamics, and drug adherence could have contributed to a more varying drug response in men, triggering the physician to use TDM. In addition, physicians may be more prone to provide men with "objective" laboratory results. Indeed, the prescribing of drugs seems to vary between male and female patients not only because of differences in morbidity.[17] Such sex-related differences in clinical practice may extend to other areas of pharmacotherapy such as the use of TDM.

Concerning the age distribution of TDM prevalence, the peak for antipsychotics in the adulthood may not be too surprising. Psychotic diseases often emerge during these years,[18] and the tailoring of treatment may therefore be most intensive during this period. However, drug–drug interactions, concomitant diseases, and deteriorating renal function all contribute to less predictable pharmacokinetics in the elderly, and the infrequent use of TDM in patients older than 60–65 years of age may represent an area of particular concern.

CONCLUSIONS

This study shows that the prevalence of TDM in clinical practice is low for antipsychotics and even lower for antidepressants. TDM is increasingly used for antipsychotics but not for antidepressants. The prevalence of TDM tends to be greater for drugs where TDM is strongly recommended. Finally, TDM is more often undertaken in men than in women, and this tool is rarely taken advantage of in older patients.

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