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Differences in antipsychotic prescriptions between centres in young outpatients with schizophrenia

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Letter to the editor:

We know that there is a gap in life expectancy between the general population and people with severe mental disorders (SMD) (1), and therefore major efforts are invested to improve physical health in this group. We welcome this development, and will add to the discussion that an important part of these efforts is to disseminate evidence based guidelines on psychopharmacological treatment because adverse effects of antipsychotic treatment are well known risk factors for many physical disorders (2). Deliberate choice of antipsychotic treatment is essential to minimize negative impact on physical health. The Schizophrenia Patient Outcomes Research Team in the US has made recommendations based on extensive review of literature (3), and the British Association for Psychopharmacology has recently published guidelines considering both efficacy and risk of adverse effects from antipsychotic treatment together with handling of these (4). In Denmark national guidelines for antipsychotic treatment were made by an expert group based on evidence of both efficacy and safety (5). According to these guidelines most patients with psychotic disorders should be treated with atypical antipsychotics (amisulpride, aripiprazole, lurasidone, paliperidone, quetiapine or risperidone) because of their favorable balance between efficacy and safety. After treatment failure on two different of the aforementioned atypical antipsychotics, monotherapy with clozapine as third line drug should be considered, unless it is not a suitable option for safety reasons. In cases where clozapine is not an option, other atypical antipsychotics (olanzapine, sertindole or ziprasidone) or typical antipsychotics (haloperidol, perphenazine or zuclopenthixole) should be considered. Only hereafter antipsychotic polypharmacy is considered a rational choice, in order to lower the psychotic symptoms. We sense, from everyday clinical practice, that this sequence is not always the case, but have so far not had any real-life data in support of this. A recent paper in this journal by Edlinger and colleagues (6) identified differences in prescription patterns between patients in in- and outpatient settings, and in another recent study Joshi and colleagues (7) documented a high degree of psychotropic polypharmacy, especially antipsychotic, among individuals with schizoaffective disorder. We have also learned some interesting aspects of antipsychotic prescription practice among outpatient units during a large scale quality program aiming at improving general health of patients with SMD (8-9); and further to implement new research-generated knowledge into clinical practice (10). In this program detailed information on all prescriptions were collected from case records and clinical interviews. The focus of the present paper is to document antipsychotic prescription practice, as this is

a potentially modifiable risk factor for physical disorders, that are within the hands of us as psychiatrists.

We had access to data from 118 consecutively referred young outpatients with schizophrenia: 69 from center A and 49 from center B, both of them in the Region of Central Denmark. All patients were diagnosed with schizophrenia, and the cohorts were similar in age (Median age 25 vs 23 years) and gender distribution (Male 64 vs 63%). We found remarkable differences among these patients concerning prescription patterns even though the two different outpatient psychosis units were organized in the same administrative region, treating similar patients, and operating under the same prescription guidelines. We found that the median total dose of antipsychotic medication was significantly higher at center A at the beginning of treatment (index) (1.58 vs 1.33 DDD, $p=0.02$, Mann-Whitey U test (see figure 1, part a)). At the final consultation within this project (follow-up) this difference in median total doses was still present, but no longer to a significant degree (1.32 vs 1.07 DDD, $p=0.52$, Mann-Whitey U test (see figure 1, part a)).

Most patients were subject to antipsychotic monotherapy as recommended, both at index (72% vs 78%) and at follow-up (58% vs 82%). We found that a higher proportion of the patients at center A were subject to antipsychotic polytherapy at index than at center B (25% vs 16%, $p=0.24$, X^2 -test (see figure 1, part b)). At follow-up this difference had increased to a significant level (32% vs 6%, $p<0.01$, X^2 -test (see figure 1, part b)). A small proportion of patients were not subject to antipsychotic treatment at these time points (3-6% at index and 10-12% at follow-up). With the "drugs of choice" from the Danish national guideline in mind, we examined the specific antipsychotics prescribed.

Recommended 1st and 2nd line antipsychotics were among the most frequent prescriptions at both centres, with aripiprazole (45%), quetiapine (44%), paliperidone (33%), and risperidone (29%) as the most commonly prescribed drugs. Amisulpride were only prescribed in 4% of patients and lurasidone were not used in any of the patients despite the relatively low risk of metabolic disturbances. Among all patients receiving antipsychotic polytherapy 49% of the patients received a combination of 1st line drugs, 43% a combination of 1st and 3rd line drug and only 8% a combination of 3rd line drugs. The combination of aripiprazole and quetiapine was the most common among first line drugs, and in combinations involving third line drugs olanzapine were the most common. The practice of prescribing antipsychotics "PRN" ("as needed") was particularly common at Center A. At both centers quetiapine was the most commonly prescribed drug in flexible

dosing (54% vs 14%). Chlorprothixene is not mentioned in the national guidelines, but was used for a considerable amount of patients, mostly in flexible, low dosing (23% vs 10%). We expected this practice as quetiapine and chlorprothixene are often used in low (sub-schizophrenia) doses to treat anxiety or agitation, but the difference between centers was remarkable (74 vs 31% of patients at any time, $p < 0.01$, X^2 -test). These kinds of prescriptions might be a considerable and relevant hidden exposure to antipsychotic drugs: For instance a common side effect from quetiapine is to exaggerate hyperglycemia. Very few patients were exposed to typical antipsychotics as perphenazine or zuclopenthixole at both centers. Olanzapine was the most frequently used 3rd line drug (22% vs 20%), and the share of patients treated with other recommended 3rd choice drugs was strikingly different between centers, even though not to a significant degree: Clozapine (10% vs 2%, $p = 0.09$, X^2 -test), sertindole (8% vs 2%, $p = 0.16$, X^2 -test). We have tested relevant patient data for other explanations to the differences: Neither gender nor age had any predictive value. Median time since first contact with psychiatry (4.22 vs 3.45 years, $p = 0.46$, t-test), and proportion of patients receiving antipsychotic treatment as intramuscular injection (38% vs 29%, $p = 0.31$, X^2 -test), which could both indicate a poorer prognosis for one of the groups, did not differ significantly between centers.

These findings suggests that there is a component of personal style, routine or habit among the psychiatrists in the prescription of antipsychotics, as some of our findings deviate from national recommendations: In treating similar patients one center uses higher doses and more polytherapy without any clear indication of more severely ill patients. Many patients are also exposed to third line drugs with higher frequency of metabolic disturbances, such as olanzapine. We support keeping a continuous focus on identification and treatment of physical health in patients with SMD, including increased attention to an optimal antipsychotic treatment in order to minimize the negative impact of side-effects. We propose continuous and mandatory post-graduate training in psychopharmacology for psychiatrists as a solution to this potential problem.

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Figure: Comparison between centres of (A) total prescribed dose of antipsychotic drugs per patient in World Health Organization Defined Daily Doses (DDD), and (B) proportion of no antipsychotic prescriptions, antipsychotic monotherapy, and antipsychotic polytherapy. Mean doses are compared by Mann-Whitney U test, and portions of polytherapy are compared by X²-test with 1 degree of freedom.

