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Effectiveness of Prescription-Based CNS Stimulants on Hospitalization in Patients With Schizophrenia: A Nation-Wide Register Study

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Objective: **Negative symptoms and cognitive deficits are main features of schizophrenia but with limited treatment options. Earlier studies have suggested that central nervous system (CNS) stimulants have a small effect on these domains, but with inconclusive results. As the first study to date, we aimed to investigate whether CNS stimulants improve naturalistic outcomes (psychiatric admissions and antipsychotic use) in patients with schizophrenia.** ***Methods:*** **By using extensive health registers all patients with schizophrenia and their use of CNS stimulants in Denmark were identified. Two models were used to investigate the effectiveness of CNS stimulants in patients with schizophrenia between 1995 and 2014; a mirror-image model with 605 individuals, using paired *t* tests and Wilcoxon signed rank tests, and a follow-up study with 789 individuals, using a conditional risk-set model.** ***Results:*** **CNS stimulants use was associated with a reduction in number of psychiatric admissions from 3.43 (95% CI = 2.86 to 4.01) to 2.62 (95% CI = 1.99 to 3.25) (*P* = .009), with a more pronounced reduction for women (mean difference: −1.37, 95% CI = −2.34 to −0.40, *P* = .006). Psychiatric bed-days were reduced by 40 (95% CI = 24.5 to 55.6, *P* < .001) for individuals with at least 1 admission before CNS stimulant use. In addition, the total amount of antipsychotic use (Defined Daily Dose [DDD]) was reduced (*P* = .001). The Hazard rate ratio in psychiatric admissions between women taking CNS stimulants compared to women not taking CNS stimulants was 0.77 (95% CI = 0.67 to 0.88). Conclusion: CNS stimulants may have clinical potentials for improving functional outcomes in patients with schizophrenia and randomized clinical studies evaluating this topic are warranted.**

Key words: psychiatric bed-days/psychiatric admissions/treatment effect/methylphenidate/antipsychotics/ADHD/cognitive dysfunction/negative symptoms

Introduction

Schizophrenia is a highly heterogeneous disorder with a relatively constant clinical phenotype with cognitive deficits, positive and negative symptoms as core features.[1] Although, these symptoms have been recognized for decades, treatment guidelines have focused on managing the positive symptoms, such as hallucinations, delusions, and disorganized thoughts by using antipsychotics.[2,3] As antipsychotics only have modest or no effect on the concomitant cognitive deficits and negative symptoms, the treatment of these domains has often been neglected.[4,5] However, negative symptoms and cognitive impairment maybe at least as invalidating for the patient as the positive symptoms,[6,7] as they often tend to have a more chronic course than the relapsing positive symptoms, and therefore have a more devastating effect on functional outcomes, underpinning the need for efficient treatments against these less amenable symptoms.

As a result, the management of cognitive impairment and negative symptoms have received more attention and it has been suggested that central nervous system (CNS) stimulants may play a role by improving cognition and thereby reducing the severity of the negative symptoms.[8–10] However, the effect sizes have been modest, but these studies have used symptom rating scales to detect an improvement of the negative symptoms, which may not reflect any beneficial effect on naturalistic outcomes, such as psychiatric admissions and bed-days.

CNS stimulants are drugs that excite the CNS by either decreasing the reuptake or increasing the release of monoamines, such as dopamine and norepinephrine. However, as most CNS stimulants increase the availability of the synaptic dopamine in the limbic system, they may increase the risk of an aggravation of the positive symptoms.[1,11] With this risk in mind, we aimed to investigate

the safety and effectiveness in schizophrenia patients that have received CNS stimulants in Denmark.

Methods

The Registers

The Danish Civil Registration Register (DCRS)[12] was established in 1968 and contains information on all individuals who were alive and living in Denmark in 1968 and onwards. The DCRS[12] utilizes a unique personal identification number, which enables accurate linkage between all administrative national registers. The Danish Psychiatric Central Research Register (DPCR) contains information on all admissions to psychiatric facilities since 1969 and all outpatient contacts after 1994.[13] The Danish National Prescription Registry (DNPR) contains information on every individual purchase of prescribed medicine since 1995.[14]

Study Population and Design

We used the DCRS and the DPCR to identify all individuals in Denmark with a schizophrenia diagnosis (ICD8: 295, ICD10: F20) and the DNPR to identify patients with schizophrenia receiving CNS stimulants. We used 2 models to assess the effect of CNS stimulants in patients with schizophrenia, a mirror-image model and a conditional risk-set model. The mirror-image model included patients with schizophrenia redeeming at least 1 prescription of CNS stimulants between January 1, 1995 and September 1, 2012 in order to allow 2-years of follow-up after first prescription of CNS stimulants. For the conditional risk-set model the entire population of patients with schizophrenia were followed from December 31, 1994 or schizophrenia onset, whichever occurred last, until dead or end of the study, on September 1, 2014.

Exposure, Outcome Measures and Explanatory Variables

Exposure to CNS stimulants included use of any of the medications in the Anatomical Therapeutic Chemical (ATC) group N06BA—except atomoxetine (N06BA09) as this is not associated with the risk of psychosis. During the study period the following stimulants were available in Denmark, amphetamine (N06BA01), dexamphetamine (N06BA02), methylphenidate (N06BA04), modanifil (N06BA07) and lisdexamphetamine (N06BA12). For the conditional risk-set model we used number of psychiatric admissions as the outcome measure. For the mirror-image model, the number of psychiatric admissions, psychiatric bed-days and antipsychotic use (ATC: NO5A except lithium (N05AN01)) were used as outcome measures. Antipsychotic exposure was defined as Defined Daily Dose (DDD) divided by days not admitted to a psychiatric facility, as medications is provided by the psychiatric ward during in-patient status. Somatic comorbidity was based on the 19 different conditions present in the Charlson comorbidity Index,[15] epilepsy (G40-41) and hepatic encephalopathy (K72). Concomitant medication use included selective serotonin reuptake inhibitors (SSRIs) (ATC: N06AB), tricyclic antidepressants (TCAs) (ATC: N06AA), benzodiazepines (ATC: N05BA and N03AE01), first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs).

In the mirror-image study, we used a 2-year mirror-image model with equal mirror-image periods to assess the effectiveness of CNS stimulants in patients with schizophrenia. The post-mirror-image period was defined from the filling of the first CNS stimulant prescription, named the index date, and ended maximum 2 years later. The post-mirror-image period was shortened if the patient died or stopped redeeming prescriptions. Individuals were characterized as not redeeming prescriptions for the whole period, if the individual did not receive a receipt on CNS stimulants in the period from 3 months before end-date until 3 months after end-date. If this was the case, the post-mirror-image period was reduced to 3 months after the last prescription.

The post-mirror-image period was mirrored around the index date. Both mirror-image periods were shortened if the patients were not diagnosed with schizophrenia at the time of pre-mirror-image period, meaning that the pre-mirror-image period was redefined as from the date of schizophrenia onset until CNS stimulant prescription and with an equally long post-mirror-image period. If redeeming of the first prescription occurred within 7 days after the discharge from a psychiatric hospital, the admission period before index was excluded from the pre-mirror-image period, as the stimulants most likely had been initiated during admission.

Statistical Analysis

In the mirror-image model, we compared number of admissions to a psychiatric facility, number of psychiatric bed-days and antipsychotic use maximum 2 years before and maximum 2 years after the first prescription of CNS stimulants. This was first performed for the overall cohort and afterwards stratified by sex. As patients admitted more often to a psychiatric facility may represented a more severe patient group, we conducted as subgroup analysis excluding patients with no admissions in the pre-mirror-image period, to address whether CNS stimulants were differently tolerated in this selected patient group. Normality was checked with Bland-Altman- and QQ-plots and the comparison was done with a paired *t* test. As number of bed-days did not satisfy the assumptions for a paired *t* test, the comparison was done by a non-parametric test, a Wilcoxon-signed rank test.[16] All tests used were double sided, and a $P < .05$ was considered statistically significant.

In the conditional risk-set analysis the entire schizophrenia population in Denmark was followed from December 31, 1994 or at the time of onset of schizophrenia, if this occurred after December 31, 1994, until dead or end of the study, on September 1, 2014. A conditional risk-set model,[17] using time to each event measured from entry, was performed to compare number of psychiatric admissions between patients with schizophrenia taking CNS stimulants and patients with schizophrenia not taking CNS stimulants. All patients receiving CNS stimulants were considered unexposed until first CNS stimulant prescription, in order to avoid immortal bias. If the patient stopped redeeming CNS stimulants, the patients was considered unexposed again from 3 months after last prescription. Each individual was censored during admission to a psychiatric facility and reentered at discharge. At the end of study, the rate of admissions was compared between the patients with schizophrenia taking CNS stimulants and patients not taking CNS stimulants. In subsequent analyses, we adjusted for antipsychotic use, age of schizophrenia onset and age at start of the follow-up. All analyses were stratified by sex.

In additional analyses we compared concomitant medication between the mirror-image periods with a McNemar's exact test.

Results

Characteristics of the Danish Schizophrenia Population

Within the study period we identified a total of 50 180 patients with schizophrenia, of which 1438 (2.87%), received CNS stimulants within the study period. Out of these, 649 (45.13%) had CNS stimulants initiated before the onset of schizophrenia and were excluded from further analysis. The remaining 789 were included in this study, of whom 605 were eligible for the mirror-image study (due to an earlier end-date, September 2012). The median time of follow-up was 465 days (25–75 percentiles = 121 and 730.5). 75 individuals (12.40%) did only receive 1 prescription of CNS stimulants before discontinuation. Patients with schizophrenia taking CNS stimulants exhibited a higher prevalence of total somatic comorbidity (78.96% vs 67.67%) and antipsychotic use (93.54% vs 77.53%) than those not taking CNS stimulants (table 1). The mean time to discontinuation was 872 days for the 789 patients receiving CNS stimulants. At the date of first CNS stimulants prescription, 400 (50.70%) of these patients were receiving early retirement pension and 601 (76.17%) of the patients were living alone. In addition, 58 (7.35%) of the patients were long-term institutionalized at the time of first CNS prescription. In the 789 patients receiving CNS stimulants, 241 (30.54%) had a concomitant diagnosis of ADHD, with 79 (28.83%) individuals among the women and 162 individuals (31.46%) among the men having concomitant ADHD.

Mirror-Image

Out of the 605 included patients, 92.89% received methylphenidate, 6.61% received modanifil, 0.33% received dexamphetamine and 0.17% received amphetamine. The mean doses were 39.7 mg, 105.2 mg, 16.7 mg and 5.6 mg for methylphenidate, modanifil, dexamphetamine and amphetamine, respectively. Overall, CNS stimulants did not significantly reduce the number of psychiatric admissions for all patients with schizophrenia (P = .369), but

Table 1. Basic Characteristics of the Total Danish Population of Patients With Schizophrenia Stratified by Whether the Patient With Schizophrenia Receives CNS Stimulants

	CNS Stimulant Medication	
Characteristics of Cohort	Taking CNS Stimulants	Not Taking CNS Stimulants
Number of individuals (*N*)	789	48 742
Mean age at end of study	37.6	52.7
Women (%)	274 (34.73%)	20 943 (42.97%)
Somatic comorbidity (%)[a]	623 (78.96%)	32 986 (67.67%)
Cardiovascular diseases (%)[b]	21 (2.66%)	4007 (8.22%)
Diabetes I and II (%)	31 (3.93%)	3616 (7.42%)
Chronic pulmonary disease (%)	124 (15.72%)	5194(10.65%)
Liver disease (%)	58 (7.35%)	2169 (4.45%)
Moderate to severe renal disease (%)	609 (77.19%)	28 949 (59.39%)
Any tumor (%)[c]	23 (2.92%)	4235 (8.69%)
Antipsychotic use after 1995	738 (93.54%)	37 788 (77.53%)

Note: CNS, central nervous system. Table 1 presents the characteristics of the Danish schizophrenia population, subdivided into two groups: a group taking CNS stimulants and a group not taking CNS stimulants.
[a]Including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer, liver diseases, diabetes I and II, hemiplegia, renal diseases, leukemia, lymphoma, any tumor, metastatic solid tumor and AIDS.
[b]Including myocardial infarction, congestive heart failure and peripheral vascular disease.
[c]Including leukemia and lymphomas as well.

there was a tendency for a better response in women ($P = .084$) compared to men with schizophrenia ($P = .986$) (table 2, second column). However, when only including patients with at least 1 admission in the pre-mirror-image period, a reduction in number of admissions from 3.43 (95% CI = 2.86 to 4.01) to 2.62 (95% CI = 1.99 to 3.25) was found ($P = .009$). This reduction was also more pronounced for women, who had a reduction in psychiatric admissions from 3.91 (95% CI = 2.86 to 4.97) to 2.54 (95% CI = 1.33 to 3.75) ($P = .006$) (table 2, third column). We were not able to quantify the difference in psychiatric bed-days for all patients with schizophrenia taking CNS stimulants, but the difference was highly significant ($P < .001$) (table 2, fifth column). However, if only patients with schizophrenia who had at least 1 bed-day prior to CNS stimulant use were included, there was a reduction by 40 psychiatric bed-days (95% CI = 24.5 to 55.6, $P < .001$) (table 2, sixth column). When stratifying on sex, a reduced number of psychiatric bed-days were found for both men and women (table 2, fifth column).

Table 2 also shows antipsychotic use. There was a significant reduction in antipsychotic (DDD) use overall ($P = .001$), with a more pronounced reduction for women taking CNS stimulants ($P = .002$) (table 2, second column)

Patients With Schizophrenia Taking CNS Stimulants vs the Entire Schizophrenia Population

Table 3 shows hazard rate ratios between patients with schizophrenia taking CNS stimulants and patients with schizophrenia not taking CNS stimulants. A total of 43 467 patients with schizophrenia were followed for 421764.34 years. Women with schizophrenia taking CNS stimulants had a significantly lower risk of readmission to a psychiatric facility compared to women with schizophrenia not taking CNS stimulants (hazard rate ratio: 0.77, 95% CI = 0.67 to 0.88). Adjustment for antipsychotic use, age of schizophrenia onset or age at start of follow-up did not attenuate this (table 3). Men with schizophrenia taking CNS stimulants did not have any significant change in psychiatric admissions compared to men with schizophrenia not taking CNS stimulants (hazard rate ratio: 1.00, 95% CI = 0.91 to 1.11) (table 3).

Side Effects and Concomitant Medication in the Post-Mirror-Image vs Pre-Mirror-Image Period

Serious adverse effects were relatively rare during CNS stimulants use. Development of seizures or epilepsy occurred in 3 (0.51%) individuals in the post-mirror-image period compared to 8 (1.37%) individuals in the pre-mirror-image period. Similar findings were made for acute myocardial infarction (1 [0.17%] vs 0 [0%]), renal disease (4 [0.68%] vs 3 [0.51%]), cerebrovascular disease (0 [0%] vs 3 [0.51%]) and hepatic encephalopathy (1 [0.17%] vs 0 [0%]). The number of patients receiving SSRIs, benzodiazepines, low-dose first-generation antipsychotics, risperidone and ziprasidone were significantly decreased in the post-mirror-image period compared to the pre-mirror-image period (table 4).

Table 2. A 2-year Mirror-Image Study Investigating the Effectiveness of CNS Stimulants in Patients With Schizophrenia

	Pre-Mirror-Image Period	Post-Mirror-Image Period	Difference in Mean (95% CI)	*P* Value
Number of psychiatric admissions for all patients with schizophrenia (SD) ($N = 604$)[a]	1.22 (3.012)	1.11 (3.047)	−0.10 (−0.33; 0.12)	.369
Men ($N = 398$)	1.16 (2.930)	1.16 (2.979)	0.003 (−0.29; 0.29)	.986
Women ($N = 206$)	1.33 (3.168)	1.02 (3.178)	−0.31 (−0.65; 0.04)	.084
Number of psychiatric admissions for patients with schizophrenia who have been admitted in the pre mirror-image period (SD) ($N = 214$)[a]	3.43 (4.246)	2.62 (4.669)	−0.82 (−1.43; −0.21)	.009
Men ($N = 144$)	3.20 (4.153)	2.65 (4.472)	−0.54 (−1.33; 0.23)	.166
Women ($N = 70$)	3.91 (4.422)	2.54 (5.081)	−1.37 (−2.34; −0.40)	.006
Psychiatric bed-days for all individuals with schizophrenia ($N = 605$)[b]				
Median (25–75 percentiles)	0 (0; 18)	0 (0; 5)	x	<.001
Psychiatric bed-days for individuals with schizophrenia with at least 1 bed-day in the pre-mirror-image period (SD) ($N = 228$)[a]	78.3 (103.29)	38.3 (80.86)	−40.0 (−55.6; −24.5)	<.001
Men ($N = 155$)	80.6 (109.18)	44.1 (90.51)	−36.5 (−57.6; −15.4)	<.001
Women ($N = 73$)	73.6 (90.04)	26.1 (53.27)	−47.5 (−66.0; −28.0)	<.001
Antipsychotic use in defined daily dose (SD)[a] ($N = 605$)	0.731 (1.370)	0.625 (1.147)	−0.106 (−0.171; −0.042)	.001
Men ($N = 399$)	0.732 (1.375)	0.664 (1.185)	−0.068 (−0.147; 0.012)	.094
Women ($N = 206$)	0.731 (1.363)	0.550 (1.067)	−0.181 (−0.293; −0.069)	.002

Note: CNS, central nervous system.
[a]Paired *t* test was used.
[b]Wilcoxon Ranksum test was used.

Table 3. Hazard Rate Ratio in Psychiatric Admissions Between Patients With Schizophrenia Taking CNS Stimulants Compared to Patients With Schizophrenia not Taking CNS Stimulants

	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)[a]	Adjusted Hazard Ratio (95% CI)[b]	Adjusted Hazard Ratio (95% CI)[c]
Men	1.00 (0.91–1.11)	1.00 (0.90–1.11)	0.97 (0.88–1.08)	0.95 (0.86–1.06)
Women	0.77 (0.67–0.88)	0.77 (0.68–0.89)	0.73 (0.64–0.84)	0.72 (0.63–0.83)

Note: CNS, central nervous system.
[a]Adjusted for antipsychotic use.
[b]Adjusted for age of schizophrenia onset.
[c]Adjusted for age at start of follow-up.

Table 4. Concomitant Medications in the Mirror-Image Periods

	Medication Use Before CNS Stimulant Medication	Medication Use During CNS Stimulant Medication	*P* Value
FGAs			
Low-potency[a]	210 (34.71%)	158 (26.11%)	<.001
Mid-potency[b]	54 (8.93%)	42 (6.94%)	.073
High-potency[c]	28 (4.63%)	26 (4.30%)	.851
SGAs			
Amisulprid	14 (2.31%)	8 (1.32%)	.180
Aripiprizol	113 (18.68%)	109 (18.02%)	.708
Clozapine	30 (4.96%)	25 (4.13%)	.332
Olanzapine	108 (17.85%)	100 (16.53%)	.374
Quetiapine	162 (26.78%)	164 (27.11%)	.928
Risperidone	106 (17.52%)	79 (13.06%)	<.001
Ziprazidone	43 (7.11%)	25 (4.13%)	.001
TCAs	32 (5.29%)	22 (3.64%)	.0525
SSRIs	212 (35.04%)	170 (28.10)%	<.001
Benzodiazepines	252 (41.65%)	231 (38.18%)	.035

Note: SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics; CNS, central nervous system.
[a]Including chlorpromazine, chlorprothixene, levomepromazine, melperone, pipamerone, and sulpiride.
[b]Including periciazine, perphenazine, prochlorperazine, and zuclopenthixol.
[c]Including flupentixol, fluphenazine, haloperidol, and pimozide.

Discussion

Main Findings

To the best of our knowledge, this is the first study that investigates the effectiveness of prescription based CNS stimulants in patients with schizophrenia in a large scale using naturalistic outcome measures, such as psychiatric admissions, psychiatric bed-days and antipsychotic use. Although, CNS stimulant use is not recommended in any treatment guidelines, as this approach is cautioned by fear of aggravating psychotic symptoms, we identified 789 patients with schizophrenia having CNS stimulants prescribed. We found a significantly overall reduction in the number of psychiatric bed-days in patients with schizophrenia treated with CNS stimulants. In addition, we found a reduced number of psychiatric admissions and use of antipsychotics in females treated with CNS stimulants. Finally, we found a reduced number of psychiatric admissions in a psychiatric facility in women with schizophrenia taking CNS stimulants compared to all women with schizophrenia in Denmark. These findings are in discrepancy with the finding of only a modest effect size of CNS stimulants on negative symptoms in other studies.[10,18,19] However, whereas these studies focused on negative symptoms by using different rating scales, we used naturalistic outcomes, which might be a proxy for other underlying patterns of schizophrenia that may be improved by CNS stimulants.

CNS Stimulants and Schizophrenia—What Do We Know?

Negative symptoms and cognitive deficits have been of great interest in recent literature. As development of new drugs for these symptoms have been limited, most of the emphasis of studies have been on existing psychoactive drugs.[11,20] In conjunction with this, CNS stimulants have been suggested.[10] Some of the CNS stimulants have resulted in a small, but significant, improvement in cognition and negative symptoms without exaggerating

positive symptoms.[10,18,19] The effect has mainly been measured by using different symptom rating scales, such as the Negative Symptoms Rating Scale. However, none of the studies have focused on naturalistic outcomes, such as psychiatric admissions and psychiatric bed-days, which most definitely can be conceptualized as a proxy for the mental status of the patients. The findings from this study suggest that even though the effect of CNS stimulants may only have a small effect on cognition and negative symptoms, it may have a beneficial effect on the overall function of the patient with schizophrenia receiving it, as the number of psychiatric admissions and psychiatric bed-days are significantly decreased. This is not only beneficial for the individual with schizophrenia, but as well for the health and social welfare systems that are imbued by the high financial burden of caring for patients with schizophrenia when they are admitted.[21]

As dopamine is believed to be the main component in the genesis of psychotic symptoms in schizophrenia,[22] it may seem inconsistent why CNS stimulants, which in different ways increase dopamine in the brain,[23] do not seem to enhance positive symptoms and thereby indirectly hospitalization rates in patients with schizophrenia. However, the current view is that schizophrenia is characterized by excess dopamine in the midbrain and substantia nigra, resulting in positive symptoms, while deficits in dopamine are seen in the prefrontal cortex.[24] As some CNS stimulants, such as modanifil, may only increase dopamine in the prefrontal cortex,[10,25] this could explain why the positive symptoms are not exacerbated. In addition, as hypodopaminergic mechanism in the prefrontal cortex has been suggested to underlie the cognitive deficits and negative symptoms of schizophrenia,[5,26,27] this could also explain why patients with schizophrenia might derive benefit in these symptoms from CNS stimulants. However, as CNS stimulants only seem to have a modest effect on negative symptoms and cognitive deficits in patients with schizophrenia, our results most likely cannot solely be explained by a reduction in these symptoms. However, our results might suggest, that treatment with CNS stimulants in patients with schizophrenia has a positive effect on the global function in the patient, which reduces the need for hospitalization, but the exact feasible explanation for this reduction is unknown and cannot be extrapolated with our study.

This leads to the question why we found a sex difference in the response to CNS stimulants. Women seem to react better to CNS stimulants and show a significantly reduced rate of all outcome measures after CNS stimulants. This is not a new phenomenon, as women have earlier been shown to react differently to drug stimulant use compared to men, which have been suggested to be due to sex differences in the neural system mediated by ovarian hormones.[28] This has especially been investigated in rats, in which CNS stimulants have shown different responses in dopamine transporters (DAT) and dopamine receptor availability and different dopamine receptor expression levels, especially in ventral tegmental area and nucleus accumbens, between sexes.[29] On the contrary, females with ADHD are at greater risk of developing schizophrenia than males with ADHD, which might suggest, that CNS stimulants may improve functional outcomes better in females due to improvement in underlying ADHD patterns.[30] However, a similar proportion of men and women in the cohort had concomitant ADHD, which makes this explanation unlikely. What the likely explanation for the difference in CNS stimulants effect between genders is unknown and will require further research.

Strengths and Weaknesses

This is the first study that investigates the effectiveness of CNS stimulants in patients with schizophrenia in a large scale using naturalistic outcome measures. The main strength is the large sample size and that we included all patients treated with CNS stimulants, not only those eligible for participating in a clinical trial where informed consent is warranted. In addition, we used more naturalistic outcome measures, which more likely cover the overall effects of CNS stimulants; in contrast to earlier studies using scales in the measurement of the effect of CNS stimulants, which may be affected by practice effect and are dependent of the mood of the particular day.[31] Finally, we investigated the effectiveness of CNS stimulants by using both a mirror-image study and a follow-up study with matched controls, reaching similar conclusions.

However, our study should also be interpreted in the light of limitations. Most importantly, the study was not randomized and confounding by indication may have occurred, eg, prescribing CNS stimulants to patients with a low risk of achieving psychotic relapse. Another possibility is that CNS stimulants were prescribed to patients with a history of high degree of psychiatric hospitalizations causing a regression towards the mean effect in the post-mirror-image period. However, as we used a conditional risk set model accounting for history of hospitalization, we believe the impact of a regression toward the mean effect is only of minor importance. As we only had access to register information, we were not able to assess indication for prescribing CNS stimulants further. Prescribing CNS stimulants may be used for several speculated indications, such as treating negative symptoms in patients with low risk of psychotic relapse, or managing antipsychotic induced adverse effects such as weight gain and sedation—or it may have been used as substitution for illegal substances, such as cocaine and amphetamine.[32,33] As a consequence, we cannot rule out that the effects in this study are driven by reduced use of illegal substances rather than a direct effect of the prescribed CNS stimulants. Unfortunately, we were not able to control for this. As we did not have access to plasma levels of

antipsychotics, we cannot rule out that the effect of CNS stimulants could be ascribed to pharmacokinetic interactions between CNS stimulants and antipsychotic drugs. However, recent studies have suggested the opposite by showing that some CNS stimulants actually induce the cytochrome P450 and thereby reduce the concentration of antipsychotic drugs.[34,35] In addition, CNS stimulants may have been used for other indications, such as narcolepsy or obesity.[23] Finally, the number of psychiatric beds in Denmark have been reduced, which has also decreased the length of hospitalization. This may overestimate the effect of CNS stimulants in our mirror-image study. However, the conditional risk set model with matched controls will not be affected by this trend, and as the models reached similar conclusions, we believe this problem was partly mitigated.

We were not able to assess the compliance of neither the antipsychotics nor the CNS stimulants. As we did not find increased use of antipsychotics, we believe it is less likely that the effects of CNS stimulants were driven by an improvement of adherence to antipsychotics. A misclassification of whether patients were actually taking CNS stimulants would tend to bias the risk estimates towards unity and therefore cannot explain our findings. Regarding psychiatric diagnoses, the registers might also lack the reliability that can be obtained by experienced clinicians, however, a schizophrenia diagnosis has a high validity in the registers.[36] At last, the proportion of patients receiving CNS stimulants in Denmark were small (1.57%), which makes it difficult to generalize our findings. In this matter, it should also be noted, that the adverse events of CNS stimulants might be of far greater significance if a much larger population of individuals with schizophrenia were to take them. In addition, the dose of CNS stimulants in this study was rather low. Focus in future studies should therefore also be on adverse effects in individuals with schizophrenia treated with CNS stimulants. At last, a concern might be that the relatively proportion of concomitant ADHD might reflect that the individuals were misdiagnosed with schizophrenia at first. However, this is very unlikely, since the mean time from schizophrenia to an ADHD diagnosis was 6 years.

Conclusion

Treatment with CNS stimulants may have clinical potentials for improving functional outcomes in patients with schizophrenia. Notably, women with schizophrenia may have a more favorable effect of CNS stimulants. Despite these promising results, the evidence for using CNS stimulants is sparse and any firm recommendation cannot be made. Clearly, further investigations should focus on identifying which patients are eligible for CNS stimulants and more studies evaluating the risk and benefits of using CNS stimulants in patients with schizophrenia are warranted.

Acknowledgment

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