7. The impact of medication use and clinical characteristics on cognitive functioning in bipolar disorder

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Abstract

Objective

Attention, memory and executive cognitive functions are frequently impaired in patients with Bipolar Disorder (BD). These impairments seem to be a trait phenomenon, but may also be influenced by medication and alcohol use. Approximately one-third of BD patients use more than one drug simultaneously, known as polypharmacy. In this study, the associations between medication use as well as clinical characteristics were investigated in relation to cognitive performance in 187 euthymic BD patients.

Methods

Sociodemographic and illness characteristics, as well as medication use were related to 3 cognitive domains (i.e., attention, memory and executive function) of the Test for Attentional Performance (TAP) using multivariable regression analyses.

Results

The main finding was that the use of multiple types of medication was associated with poorer cognitive performance in all three cognitive domains, but only statistically significant for executive functioning (β= -0.19, *P*=0.004). Particularly the use of antipsychotics was associated with impaired executive functioning, whereas Lithium use was not associated with cognitive performance. As we included only euthymic patients, our findings cannot be extrapolated to chronically unstable patients.

Conclusions

Our findings suggest that the use of multiple types of medication adversely affects diverse cognitive domains in BD patients, but specifically executive functions. Clinicians should be aware of these potential side effects when prescribing medication to BD patients.

Introduction

Bipolar Disorder (BD) is a common mood disorder, characterized by mood swings like depression and (hypo) mania. In addition to mood episodes, recent evidence shows that cognitive deficits are important clinical features of BD (1) related with poorer social and global functioning. In BD, attention problems, slowing of processing speed, and deficits in working memory and executive functioning appear to be most consistently observed (2), and have negative influence on treatment adherence and outcome of the disease(3). The disturbances are partly state-dependent and partly determined by trait factors of BD that may have a genetic origin, however, cognitive performance seems mostly linked to specific sociodemographic and clinical factors like age, level of education, medication use, residual mood symptoms and early adversity (4). The impact of Lithium use on cognition appears to be minimal (5, 6), but antipsychotic use seems associated with deficits in memory and executive functioning in BD patients (5). Despite available research, little attention has been given to the cognitive side effects of the number of different types of medication, known as polypharmacy, which is common practice in the treatment of BD (7). Other clinical characteristics of BD related to cognitive performance include BD subtype (8), and with some controversy, substance abuse (9).

However, studies are small, with a number of included patients between 10 -76 (10). In this study we aimed to further disentangle the associations between cognitive performance in a large cohort of 187 BD patients, medication use and a number of sociodemographic and clinical characteristics. We hypothesize that medication use and specifically use of multiple types of medication would adversely associate with specific domains of cognitive functioning.

Patients and Methods

Study design

This is a cross-sectional study involving outpatients with BD. This study was approved by the Medical Ethical Committee (METTIG) in Utrecht, The Netherlands, and was performed in accordance with the declaration of Helsinki.

Out of a cohort existing of 364 patients with BD, a subgroup of 187 (51.4%) agreed to perform cognitive tasks. The cohort of 326 patients has been described in a previous publication (11), currently extended to 364 patients. These 187 patients fulfilled the inclusion criteria of being diagnosed with BD1, BD2, cyclothymia or BD not otherwise specified, all according DSM-IV-TR diagnosis and being older than 18 years. Due to small numbers, cyclothymia and BD no otherwise specified were included in the BD2 group in all analyses. They were all euthymic at the time of the investigation. All patients are treated in the Program for Mood Disorders at PsyQ in The Hague, The Netherlands. An exclusion criterion in this study were schizo-affective disorder and age below 18 years old. Participants were comparable with the non participants with regard to age and gender and clinical characteristics, but differed with respect to subtype of BD (respectively 66.8% and 80.4% BD1; p=.05), number of depressive episodes (median respectively 6.5 and 5; p=.02), Lithium use (respectively 27.3% and 15.7% used no Lithium; p=.006) and alcohol use (respectively 35.1% and 46.7% used no alcohol; p=.03).

Assessment of clinical characteristics and medication use

Detailed information about the protocol regarding data collection of diagnostic status and sociodemographic information, is described in our previous publication (11). In addition, to assess euthymia, all patients were questioned about current mood with the Quick Inventory of Depressive Symptomatology- Self Report (QIDS-SR) (http://www.ids-qids.org) and the Young Mania Rating Scale (YMRS) (12). Euthymia was prospectively defined as score ≤7 for the YMRS and a score of ≤12 for the QIDS-SR. Early adversity was assessed with questions of the Childhood Trauma Questionnaire (CTQ) (13).

The psychotropic medication types that were used most frequently, were coded according to the Anatomical Therapeutic Chemical Classification System (http://www.whocc.no/) and included Lithium (ATC code: N05AN01), anti-epileptics (ATC code: N03AF01, N03AG01, N03AX09) antipsychotic medication (ATC code: N05Ax with exclusion of N05AN01), benzodiazepines (ATC codes: N05BA, N05CD, N03AE01, N05CF), and antidepressants (N06A). Lithium is regarded as drug of first choice in the treatment

of Bipolar Disorder, therefore it was not included in antipsychotic medication but coded separately. In case of more than 1 used medications of the same type (for example the use of 2 antidepressants), this was counted as 1 type.

Test for Attentional Performance (TAP)

Cognitive performance was assessed by means of the Test for Attentional Performance ('Testbatterie für Aufmerksamkeitsprüfung' (TAP), version 2.1, http://www.psytest.net/ ; Zimmermann & Fimm, 2002). The TAP is a widely used computer based standardized test battery and is easy to use in clinical practice (5, 14, 15). In this study, 8 out of 12 subtests were used to evaluate cognitive performance in the patient group, including attention (phasic and tonic), sustained attention, divided attention, working memory, cross-modal integration, flexibility, go/no-go and incompatibility. The other four subtests included eye movement, visual neglect, visual field scanning and vigilance. These subtests were initially developed for patients with brain damage, but are of less interest for our research question and were therefore excluded. In previous studies raw scores as well as compound scores were used in further analyses (for references see http://www.psytest.net/). All skewed variables were log transformed to fulfill normal distribution criteria. To summarize the results in further analyses and avoid multiple testing problems, compound scores and z-scores were created and averaged for 3 domains of closely related cognitive component item test results, namely attention (11 component items, including alertness median reaction time in two series, alertness errors and total performance index; sustained attention errors in four series, sustained attention omissions in four series), working memory (2 component items: errors and omissions) and executive functioning (13 component items, including flexibility, total performance scores of 2 series, divided attention errors, omissions and correct scores in two series, go/ no go errors and median, incompatibility median and errors in two series, cross modal integration errors and omissions). Intercorrelations between the component items of each compound z-score were highly significant, with the exception of two component items in the z-score for executive functioning. However, when re-analyzing the data excluding these 2 component items, results remained largely similar. Lower z-scores reflect more mistakes, longer reaction times and more omissions. Attention includes phasic and tonic attention, as well as a separate subtest for sustained attention. Executive functioning comprises divided attention, flexibility, Go/No go, incompatibility and cross modal integration.

Statistical analysis

All of the analyses were conducted using SPSS version 17.0 statistical software (SPSS Inc, Chicago, Illinois). First, analyses were performed to describe the clinical characteristics, with use of t-tests and Chi-square tests when appropriate to compare participants with non-participants. For TAP results z-scores were created, tested for normality, and used to analyze the possible relationships between domains of cognition and baseline characteristics. For assessing correlations between z-scores, Pearson's correlation scores were used. Based on linear regression analysis with z–scores as dependent variables and baseline characteristics as independent variables, we decided to use age, gender and level of education as covariates in multivariate regression analysis. Variables with positively skewed distributions (e.g., number of depressive episodes and number of (hypo) manic episodes) were logarithmic transformed for all analyses. Back-transformed geometric medians with Inter Quartile Rates are presented in the tables, when appropriate. To correct for multiple testing with 10 analyzed variables per cognitive domain (medication use; BD subtype; childhood adversity; current anxiety disorder; psychiatric co-morbidity; alcohol use; drug use; smoking; age of onset; current mood), we used the compound scores in our analyses. Results are considered significant with a p-value < .05.

Results

Clinical characteristics

In table 1 all population characteristics are summarized.

Anxiety disorder was mentioned separately, due to the high prevalence. All participants were euthymic with a mean QIDS score of 7.7 (SD=5.0), reflecting no or mild symptoms (http://www.ids-qids.org) and a mean YMRS score of 1.6 (SD=2.9), meaning no manic or hypomanic symptoms. The Pearson's correlation scores between the three cognitive domains were respectively r=.45, p<.001 (for the association between working memory and attention); r=.40, p<.001 (for attention- executive functioning); and r=.35, p<.001 (for working memory and executive functioning). Out of 187 participants, 184 (98%) completed the attention tests, 147 (79%) completed the working memory subtest and 166 (89%) completed all executive function subtests. All these patients were included, however for the in domain attention 42 patients and for the domain executive functioning 26 patients had 3 or more missing component tap items. When re-analyzing the data with exclusion of patients with >3 missing variables, effects reflected by β- coefficients were largely similar, though of slightly less strength.

On all component items of the TAP, the patient group showed longer mean reaction times with larger standard deviations, more omissions and more mistakes in comparison with persons from the general population described in the TAP manual as reference populations. They showed longer mean reaction times with larger standard deviations, more omissions and more mistakes in comparison with persons from the general population. As norm scores for sustained attention are unknown, no comparison was possible.

Table 1: *Characteristics in 187 participants with BD*

	Participants
Total N	187
Male sex; n(%)	75 (40.1)
Mean age; (SD)	48.6 (11.1)
Level of education;	
N (%):	
- primary	41 (21.9)
- secondary	55 (29.4)
- higher	91 (48.7)
Clinical characteristics:	
Diagnostic information; N(%)	
BD1	125 (66.8)
Childhood adversity	56 (30.4)
Current anxiety disorder	54 (28.9)
Psychiatric co-morbidity	75 (40.1)
Age of onset; mean (SD)	
Age of onset first (hypo-) mania	29.0 (11.9)
Age of onset first depression	24.9 (12.2)
Age of onset disease	26.7 (9.5)
Number of episodes; median (IQR)	
No. of manic episodes	5 (2-10)
No. of depressive episodes	6.5 (4-20)
QIDS; mean (SD)	7.7 (5.0)
YMRS; mean (SD)	1.6 (2.9)
Medication use; N(%):	
Lithium	
No lithium (ref)*	51 (27.3)
Only lithium	49 (26.2)
Lithium + other medication	87 (46.5)
Anti-epileptics	40 (21.4)
Anti-psychotics	43 (23.2)
Benzodiazepines	54 (29.2)
Antidepressants	64 (34.4)
No. of psychotropic med.ty pes; mean (SD)	2.1 (1.2)
Substance use; N(%):	
Alcohol use	
None	65 (35.1)
1-2 units/day	100 (54.1)
≥3 units/day	20 (10.8)
Drug use	14 (7.7)
Smoking	78 (42.2)

Abbreviations: BD indicates Bipolar Disorder; IQR indicates Inter Quartile Range; YMRS indicates Young Mania Rating Scale; QIDS indicates Quick Inventory of Depressive Symptomatology.

Influence of sociodemographic and clinical characteristics, medication use and substance use on cognition

In table 2, the sociodemographic and clinical characteristics are presented in relation to the three described cognitive domains.

Older age was significantly associated with all three cognitive domains: poorer attention (unadjusted β=-.35; p<.001), working memory (unadjusted β=-.19; p=.02), and executive functioning (unadjusted β=-.38; p<.001). Higher level of education was associated with better working memory (unadjusted β=.35; p< .001) and executive functioning (unadjusted β=.45; p<.001), but not with better attention. Mood scores on QIDS and YMRS were not associated with TAP scores. In table 3, β-coefficients with the accompanying p-values are presented, adjusted for gender, age and level of education.

With respect to clinical characteristics, we found that BD 2 was related to better attention (unadjusted β=.19; p=.009; adjusted β=.16; p=.03) and we found a trend towards better executive functioning in BD2 patients (unadjusted β=.15; p=.05; adjusted β=.11; p=.10). The number of manic episodes was also positively related to executive functioning (unadjusted β=.12; p=.13; adjusted β=.14; p=.04).

With respect to medication use, we found that the number of different types of psychotropic medication was associated with poorer performance on executive functioning (unadjusted β=-.19; p=.01; adjusted β=-.19; p=.004). When analyzed per medication type, Lithium use versus no Lithium use was not associated with cognitive function on any domain. However, when Lithium use was compared with Lithium plus other medication types, a statistical trend was observed that showed lower performance on executive functioning in the group using Lithium and other medication (unadjusted β=-.13; p=.13; adjusted β=-.19; p=.01). The use of anti-psychotics was related with lower scores on executive functioning (unadjusted β=-.22; p=002; adjusted β=-.20; p =.002). A statistically significant association was found for the use of antidepressants and lower attention scores (unadjusted β=-.16; p=.03; adjusted β=-.16; p=.02). Figure 1 shows the associations between the number of different types of psychotropic medication and cognitive function on the three domains.

When trying to gain insight in whether medication worsens cognitive function or whether the severity of illness confounded the association, all analyses with the number

of medication were additionally adjusted for severity of illness course variables age of first episode, number of depressive and number of manic episodes, QIDS score and YMRS score. Most associations persisted with beta-coefficients that did not decrease in strength.

Finally, with respect to substance use, we found an association between moderate alcohol use and attention, that remained significant after adjustment for gender, age, level of education, indicating that moderate alcohol use (of 1-2 units per day) was associated with slightly better attention versus no alcohol use. Smoking was also associated with better attention (unadjusted β=.15; p=.05; adjusted β=.16; p=.03).

Table 2: *Clinical characteristics in relation with cognitive performance in 3 domains*

	Attention (n=184)			**Working memory** (n=147)			**Executive functioning** (n=185)		
	N	b	**P**	**N**	b	**P**	**N**	b	**P**
Female (vs male gender)	111	.02	.84	90	.04	.67	111	-.07	.37
Age	184	**-.35**	<.**001**	147	**-.19**	.**02**	185	**-.38**	<.**001**
Level of education::									
- primary (ref)*	40	Ref.		25	Ref.		40	Ref.	
- secondary	55	.08	.44	44	.21	.08	55	.29	.**01**
- higher	89	.13	.15	78	**.35**	<.**001**	90	**.45**	<.**001**
Clinical characteristics									
Diagnostic information:									
BD 2 (BD 1 ref.)	122	**.19**	**.01**	101	.16	.06	123	.15	.05
Childhood adversity	54	-.08	.31	39	.01	.91	55	-.02	.82
Current anxiety disorder	55	-.10	.18	42	-.04	.65	55	.05	.55
Psychiatric co-morbidity	75	-.03	.67	61	-.04	.68	75	.07	.34
Age of onset:									
Age of onset first mania	163	-.15	.05	130	-.05	.58	164	**-.21**	**.01**
Age of onset first depression	167	**-.24**	.002	131	-.01	.94	168	-.14	.07
Age of onset disease	183	**-.21**	**.004**	146	-.05	.52	184	-.12	.10
Number of episodes:									
No. of manic episodes	163	.02	.76	130	-.01	.95	164	.12	.13
No. of depressive episodes	167	-.00	.96	131	.00	.97	168	-.01	.85
QIDS	180	-.02	.80	143	-.06	.51	181	-.04	.62
YMRS	181	-.01	.85	144	-.03	.76	182	.08	.23
Medication use:									
Lithium									
- no lithium (ref)*	50	Ref.		38	Ref.		50	Ref.	
- only lithium	49	-.02	.88	40	-.11	.36	48	-.00	.97
- lithium + other medication	85	-.06	.50	69	-.06	.57	87	-.13	.13
Anti-epileptics	38	.04	.58	30	.03	.73	40	.02	.83
Anti-psychotics	42	-.06	.44	35	-.12	.16	43	**-.22**	.**002**
Benzodiazepines	53	-.09	.25	40	-.06	.45	54	-.18	.**01**
Antidepressant	64	**-.16**	**.03**	48	-.06	.48	64	-.08	.29
No. of psychotropic med. types	184	-.10	.18	147	-.09	.30	185	**-.19**	**.01**
Substance use:									
Alcohol:									
- none (ref.)*	63	Ref.		43	Ref.		63	Ref.	
- 1-2 units/day	99	**.20**	**.01**	84	**.18**	.**04**	100	.16	.05
- ≥3 units/day	20	.09	.44	18	-.11	.40	20	.01	.96
Drug use (no drug use ref.)	14	-.08	.31	12	.08	.37	14	.12	.10
Smoking (non-smoking ref.)	77	.15	.05	61	.06	.48	77	-.02	.78

* For reference category no β can be estimated

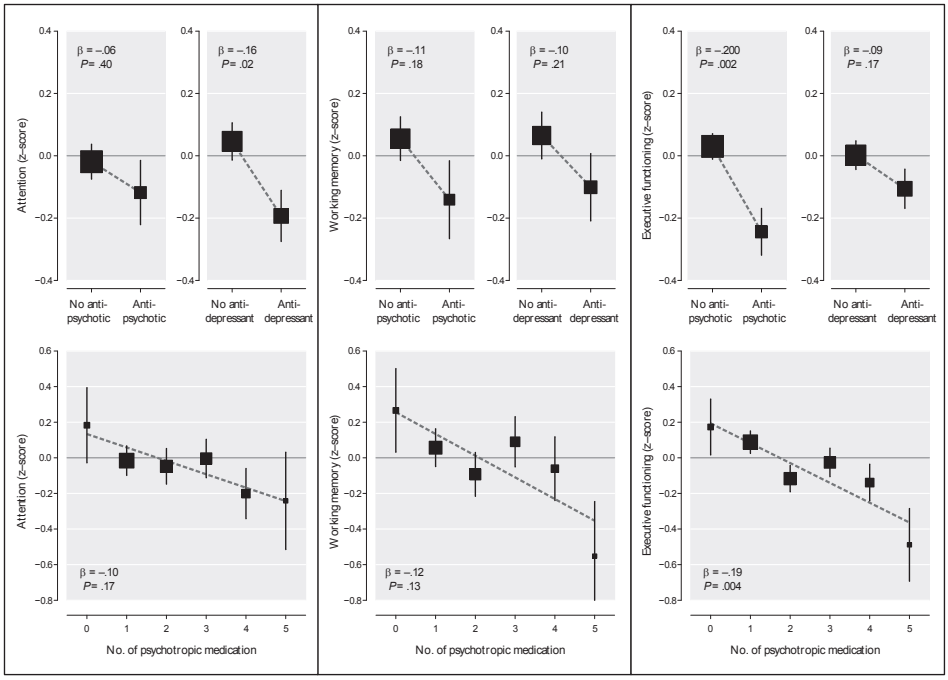
Table 3: *Clinical characteristics in relation with cognitive performance in 3 domains, adjusted for covariates age, gender and level of education*

	Attention (n=184)			**Working memory** (n=147)			**Executive functioning** (n=185)		
	N	b	**P**	**N**	b	**P**	**N**	b	**P**
Clinical characteristics									
Diagnostic information:									
BD 2 (BD 1 ref.)	59	**.16**	**.03**	45	.12	.13	59	.11	.10
Childhood adversity	54	-.10	.16	39	.03	.76	55	.01	.90
Current anxiety disorder	54	-.13	.06	42	.01	.94	55	.09	.18
Psychiatric co-morbidity	75	-.09	.24	61	.01	.95	75	.08	.24
Age of onset:									
Age of onset first mania	163	-.01	.87	130	.01	.97	164	-.03	.74
Age of onset first depression	167	-.15	.06	131	.03	.74	168	.01	.92
Age of onset disease	183	-.11	.12	146	-.03	.72	184	.02	.80
Number of episodes:									
No. of depressive episodes	167	.02	.80	131	.05	.53	168	.06	.42
No. of manic episodes	163	.02	.76	130	.04	.62	164	.14	**.04**
QIDS	180	-.02	.79	143	-.03	.72	181	.00	.99
YMRS	181	-.04	.54	144	-.04	.59	182	.06	.36
Medication use:									
Lithium use:									
- no lithium (ref)*	50	Ref.		38	Ref.		50	Ref.	
- only lithium	49	-.01	.95	40	-.07	.56	48	-.05	.58
- lithium + other medication	85	-.07	.38	69	-.07	.44	87	**-.19**	**.01**
Anti-epileptics	38	.03	.39	30	-.02	.83	40	.00	.95
Anti-psychotics	42	-.06	.40	35	-.11	.18	43	-.**20**	.**002**
Benzodiazepines	53	-.02	.75	40	-.02	.80	54	-.08	.26
Antidepressant	64	**-.16**	**.02**	48	-.10	.21	64	-.09	.17
No. of psychotropic med types	184	-.10	.17	147	-.12	.13	185	**-.19**	**.004**
Substance use:									
Alcohol use:									
- none (ref.) *	63	Ref		43	Ref		63	Ref	.40
- 1-2 units/day	99	**.16**	**.04**	84	.14	.10	100	.06	.79
- ≥3 units/day	20	.10	.35	18	-.08	.56	20	-.03	.07
Drug use (no drug use ref.)	14	.06	.43	12	.09	.25	14	.12	.85
Smoking (non-smoking ref.)	77	**.16**	**.03**	61	.08	.31	77	-.01	.74

* For reference category no β can be estimated

Figure 1.

Mean standard scores (with error bars representing standard errors) for attention (n=184), working memory (n=147), and executive functioning (n=185) in BD patients according to the use of antipsychotic medication, the use of antidepressant medication, and the total number of psychotropic medication used. The grey reference line shows the mean cognitive score. The size of each square is proportional to the number of patients. Scores are adjusted for sex, age, and education. Beta-coefficients and P values are calculated by multivariate linear regression analysis.



Discussion

We studied the relationship between cognitive performance and sociodemographic and clinical characteristics of BD, medication use and substance use. In this study we found that the non-illness related variables age and level of education were strongly associated with cognitive performance assessed with the TAP. With respect to clinical characteristics we found that BD2 is associated with better attention and more manic episodes are associated with better executive functioning. Second, the number of different types of medication was inversely associated with executive functioning, and non-significantly with poorer levels of attention and working memory. When focusing on the individual types of medication, antipsychotics were in particular associated with poorer executive functioning, while antidepressant use was associated with poorer attentional performance. Remarkably, Lithium had no influence on cognitive performance. Smoking and moderate alcohol use (1-2 units/day) was related to better attention, but was not associated with working memory or executive functioning.

Sociodemographic characteristics: Age and level of education

Age is a well known determinant of cognition, with mainly processing speed, reasoning, memory and executive functions declining with advancing age (16). This is referred to as cognitive ageing starting in early adulthood, which is in line with our results. The influence of the level of education on cognition has also been studied thoroughly in the elderly, whose educational level positive associated with late life cognition (17). This is in line with our findings that educational level was strongly associated with better cognitive performance.

Clinical characteristics

BD2 was found to be associated with a slightly better cognitive functioning on all three domains (though only significantly for attention) compared to patients with BD1. This finding was partly consistent with the findings from a meta-analysis (8), showing that BD2 patients performed slightly better only on memory tasks but furthermore the patients in this meta-analysis were equally severely impaired on other cognitive domains. Criteria to differentiate BD1 and BD2 are soft and hypomania is difficult to diagnose, leading to a risk of misclassification. For all these reasons, differences between BD1 and BD2 need to be more thoroughly studied. Regarding the influence of the number of mood episodes, it was recently found that a history with more manic and depressive episodes was associated with poorer working memory (18). However, no longitudinal studies

are available to further specify the influence of number of episodes. Our finding that number of manic episodes was positively associated with executive functioning should therefore be interpreted with caution. Longitudinal studies are needed to investigate the influence of the number of episodes.

Use of multiple types of medication

Many BD patients, even one third after one year medication use, use more than one drug simultaneously (7). In our patient group, an impressive percentage of 59.9% used 2 or more types of psychotropic medication. Kupfer et al. found that more than one third of bipolar patients even uses 3 or more different types of psychotropic medications (19). This could be explained by selection bias (see Strengths and weaknesses). Without taking into account the problematic side effects, interaction risks and health problems, use of multiple types of medication itself has previously been found to be negatively associated with cognition in 76 patients with bipolar (spectrum) disorder (18). Elie et al (20) also found negative effects on cognition in 56 patients who suffered from schizophrenia or schizoaffective disorder, possibly (partly) explained by high doses of antipsychotics. Although one explanation for the link may be that use of multiple types of medication adversely affects cognition in BD patients, the direction of causality may be more complex. It could indicate a higher degree of disease severity explaining both use of multiple types of medication and cognitive dysfunction. Another possibility is that patients with more cognitive deficits and subsequent worsening clinical outcomes, end up using more medication which may lead to use of multiple types of medication and as such to cognitive impairment. However, by adjusting our analyses for clinical severity parameters, all findings remained, thereby strengthening the hypothesis that medication use influences cognitive deficits.

Antipsychotic use and cognition

In observational research, it is not possible to completely disentangle the direction of this association. Besides a direct adverse effect of antipsychotics on cognition, it is again possible that third factors, like more severe disease activity or history of psychosis (21) could explain both the prescription of antipsychotics and poorer cognition. One argument supporting the hypothesis that cognitive deficits are adverse effects of antipsychotics is given by a recent study of Arts et al. (18), who followed cognitive performance in 76 bipolar patients over a period of 2 years. Use of second generation antipsychotics was associated with negative effects on cognition, mainly affecting motor speed and information processing. In particular antipsychotics were repeatedly correlated with worsening of cognitive performance and IQ in bipolar patients (22). Moreover, these findings seem to be rather specific for bipolar patients (5). Effects of antipsychotics in patients with schizophrenia were conflicting. However, Elie et al. (20) found that increasing antipsychotic daily doses as well as use of multiple types of medication were associated with poorer cognitive functioning.

Antidepressants and attention

Antidepressants may also be responsible for the occurrence of some of the side effects on cognitive dysfunction. Anticholinergic effects (for example resulting from the usage of paroxetine) are known to influence cognition, especially memory retrieval (23). The authors state that these effects might be even more pronounced in elderly patients. However, studies in patients with BD are scarce. In the study of Arts et al. no influence of antidepressants on cognition was found in BD patients (18). However, as antidepressants differ in pharmacological profiles it is difficult to assess this medication type as a group.

Lithium use and cognition

In our study, lithium use was not related to cognitive decline. In literature, short term and long-term use of lithium have been recognized to exert differential effects on cognition. Short term use could negatively affect processing speed (18). Subjective complaints of Lithium users clearly include mental slowness as well (24). Chronic lithium use was associated with minor (6) or no (25) cognitive problems. Recently, it has been shown that long-term lithium exposure in brain injured mice is leading to attenuation of neuronal degeneration in areas of the hippocampus (26), accompanied by improved performance in spatial learning and memory tasks during a 14 day follow-up. In human

patients with Bipolar Disorder, Arts et al. (18) also found that long term use of Lithium positively predicted longitudinal improvement in verbal learning.

Substance use

We found that smoking as well as daily alcohol use of 1-2 glasses is associated with improved attention. It is known that smoking is directly influencing the nicotinergic receptors, involved in for example attention, learning and working memory (27). Therefore, direct smoking effects cannot be ruled out. Light to moderate daily alcohol use is known to have preventive effects on (vascular) dementia (28). Our study included middle aged patients (mean age=48.6; SD=11.1). We hypothesize that light to moderate alcohol use could protect also against mild cognitive decline in these middle aged patients.

Strengths and weaknesses of this study

A strength of this study is the high number of patients compared to previous studies in BD that included a total of 10 to 76 subjects (10). Moreover, all patients were in a euthymic phase of the illness, thus ruling out the effects of current manic or depressed mood state and the median number of medication was high, suggesting a high disease severity on average. This limits the external validity of our findings and the possibility to extrapolate the conclusions to chronically unstable patients and patients with milder symptoms.

This study focuses on clinical characteristics and medication use. We are aware of the fact that other factors, for example, physical risk factors summarized in metabolic syndrome, are known to be related with worse performance on cognitive tasks (executive function, working memory) as well (29). This needs attention in future studies.

Two weaknesses should be noted. Firstly, because of the cross-sectional design, it was not possible to disentangle the direction of causality. More severe illness is likely associated to more extensive use of medication, and therefore it cannot be ruled out that disease severity rather than medication adversely affected cognition. However, antipsychotics and use of multiple types of medication are known to negatively influence cognition in other studies. In our study the findings remained alike after adjustment for disease severity parameters, suggesting a separate role for medication in influencing cognition. Secondly, selection bias is not ruled out, showed by the high percentage of patients using 2 or more different types of medications. This could have led to a more severe patient population included. Therefore, conclusions are only justified for a subgroup

of severely ill patients. Thirdly, information about the history of psychotic symptoms for example during manic episodes, was unavailable. Finally, it needs to be remarked that cognitive deficits is not automatically related with subjective cognitive complaints (30). Therefore, clinical relevance has to be further assessed in future research. It will also improve insight in clinical relevance, when it is possible to compare the cognitive performance of our group with a matched healthy control group.

Conclusion

We conclude that use of multiple types of medication, specifically with antipsychotic medication, is associated with poorer performance in three important cognitive domains in patients with BD. In the light of the aforementioned, we carefully recommend clinicians to take into account the long term side effects on cognition of antipsychotics and use of multiple types of medication when deciding about pharmacological treatment options in patients with BD.

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