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RISK AND EFFICACY IN COGNITIVE FUNCTIONS IN BIPOLAR DISORDER II WITH ATYPICAL ANTIPSYCHOTIC AUGMENTATION

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SUMMARY

BD-II has been consistently associated with cognitive dysfunction across a broad range of cognitive domains. Atypical antipsychotic drugs, or SGAs are effective antipsychotics in these diseases, often in combination with antidepressants and mood stabilizers. Data on the possible effect of antipsychotics on neuro-cognition are rare and conflicting. The main objective of our study was to assess the effectiveness and possible risks to cognitive function in a group of inpatients affected by BD-II. Forty-five inpatients with Bipolar II Disorder (DSM-5) were included in a two-year observational study. They were treated with sodium valproate as a mood stabiliser, atypical antipsychotics and SSRIs. The utilized SGA augmentation were quetiapine (n=13); aripiprazole (n=10); olanzapine (n=11); asenapine (n=11). All inpatients were administered some psychopathological scales and evaluated for neuropsychological variables (for example, attention, verbal memory domains, etc.). After two years of treatment with SGAs, there has been no significant reduction of previous levels. In particularly, quetiapine and asenapine groups showed a better performance in learning task, short-term task and recognition tasks, in accordance with previous studies. Our small observational study shown that atypical antipsychotics cause an improvement in symptoms in BD, and particularly BD II. In particular, they do not induce significant alterations in overall cognitive performance generally. On the contrary, some SGAs, such as quetiapine and asenapine, seem to demonstrate a not statistically significant mild improvement in cognition.

Key words: *bipolar disorder type II – atypical antipsychotics – cognitive deficits – effectiveness*

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BACKGROUND

Cognitive dysfunction in attention, memory and executive function occurs across a range of neuropsychiatric disorders, including schizophrenia, bipolar disorder (BD) and unipolar disorder. In recent years there has been an exponential increase in studies of cognitive dysfunction in bipolar disorder (Burdick 2015) across several domains in affected individuals even during the first episode as well as in unaffected relatives (Lee 2014). Bipolar Disorder has been consistently associated with cognitive dysfunction across a broad range of cognitive domains (Solè 2016, 2011, Bora 2011). Overall studies show that patients with bipolar disorder display cognitive dysfunction such as attention, memory, and planning difficulties, in addition to their affective symptoms (Bortolato 2015). Cognitive deficits are not only present during acute mood episodes but persist into periods of remission and impair patients' socio-occupational functioning. More recent data indicate that a large proportion of patients with bipolar disorder experience only partial recovery from affective and cognitive symptoms between episodes (Kurtz & Gerraty 2009).

The neurocognitive dysfunction in BD has been the focus of debate for many years, despite some conflicting data, some evidence suggests that there are few differences between the two main BD subtypes, bipolar I disorder (BD-I) and bipolar II disorder (BD-II) (hypomanic episodes in addition to MDE), in terms of cognition (Tsitsipa & Fountoulakis 2015, Solè 2011, Bora 2011). Particularly, BD-II has been consistently associated with cognitive dysfunction across a broad range of cognitive domains. In a recent review, the authors (Tsitsipa & Fountoulakis 2015) found the presence of neurocognitive deficits in BD, in almost all neurocognitive domains. This deficit is qualitatively similar to that observed in schizophrenia but it is less severe. However, for reasons which are unclear there are no differences between BD subtypes. Probably, there is a core deficit that is either increased or on the contrary it is attenuated by many factors such as the disease phase, specific personal characteristics of the patients (age, gender, number and type of episodes, age at onset, number of hospitalizations education, etc.), current symptomatology and its treatment and the long-term course and the long-term exposure to medication, psychiatric and somatic comorbidity and alcohol and/or substance abuse (Miskowiak 2012).

LIMITS AND DIFFICULTIES WITH COGNITIVE DEFICIT ASSESSMENT

Despite the prevalence and significant impact on patients' lives, during the different episodes of the disorder, cognitive symptoms are neither fully understood nor commonly assessed in clinical practice. Correct identification of objective cognitive dysfunction is important in the clinic for monitoring treatment effectiveness and efficacy of treatments in cognitive dysfunction (Bakkour 2014) although a common criticism to this line of research is that deficits appear to be non-specific (Martinez-Aran & Vieta 2015). However, it is extremely difficult to administer the most effective and most useful tools. Although for clinicians and

researchers there are numerous evaluation tools for cognitive assessment (Pendlebury 2015, Burleigh 2002), such tests are impractical for routine use in clinical practice because they are time consuming and may require trained professionals for administration (Fehnel 2016). Therefore, it is useful to have patient-reported outcome (PRO) measures that allow for the assessment of cognitive symptoms based on patients' perceptions and experiences in their everyday lives. BD may first present to the family doctor, as the usual age of onset is in adolescence or early adulthood. If the general practitioner is alert to these possibilities, this may help in arriving at the correct diagnosis and use of appropriate management strategies (Muneer 2016b). Indeed, recent findings highlight barriers, difficulties and inconsistencies in psychiatrists' routine clinical evaluation of cognitive function in psychiatric disorders (Belgaied 2014, Tavormina 2007). All this leads to a poor rate of use of cognitive assessment instruments with their own patients in clinical practice. In BD, psychiatrists rely more often on the patient history interview (63%). The key point is the need to apply an assessment of cognition that can try to achieve the objective in a simple and effective manner (Svendsen 2012). And that the availability of simple and handy tools can be crucial for good clinical practice (Russo 2015).

ANTIPSYCHOTICS TREATMENT AND COGNITIVE DEFICITS

SGAs are a heterogeneous class of medications that over the past several years, have been used increasingly in the management of bipolar disorder, particularly for acute mania (Altamura 2013, Vieta 2005, Sachs 2000). The available data suggest that atypical antipsychotics are more effective than placebo for the treatment of acute mania and maintenance of bipolar disorder, and even more effective when combined with lithium or valproate (Muneer 2016, Geddes 2013, Hirschfeld 2012, El-Mallakh 2010). Four of these therapies - olanzapine, quetiapine, ziprasidone, and aripiprazole – subsequently received approval for the maintenance treatment of bipolar disorder. The data on the possible deleterious effect of antipsychotics on neurocognition are rare and conflicting (Tsitsipa 2015, Goldberg 2009, Holmes 2008). In bipolar disorder, the positive effects of drugs on mood and psychotic symptoms may carry some indirect positive impact on cognition, but also cognitive side-effects related to extrapyramidal, sedative, anticholinergic, and blunting mechanisms of drugs such as lithium, anticonvulsants or antipsychotics.

The aims of our study was to examine the use of some second-generation antipsychotics (aripiprazole, asenapine, olanzapine, quetiapine) for bipolar disorder in clinical practice, both overall and their effects on cognitive functions in inpatients with Bipolar II disorder.

METHODS

Forty-five inpatients were included in a two-year observational study, recruited in the Neuropsychiatric Centre "Villa dei Pini" of Avellino, Italy. At the beginning, we have included in the observational study fifty-three inpatients, affected by Bipolar II Disorder (DSM-5). All inpatients were mood stabilised with sodium valproate, one atypical antipsychotic (SGAs), and SSRIs (paroxetine, sertraline). Only 45 inpatients finished the study. The main inclusion criteria were: onset of the disease less than two years; age between 18 and 65 years; written permission for administration of the scales. The study was conducted in patients hospitalized from 2013 to 2016, and evaluated for 24 consecutive months. Discharged patients were observed in subsequent clinical interviews in normal clinical practice. The data collected were: age, gender, educational level, number and type of episodes, age at onset, number of hospitalizations, age of illness. The augmentation SGAs were quetiapine (n=13); aripiprazole (n=10); olanzapine (n=11); asenapine (n=11). Clinical symptomatology at the time of assessment (depressive episode or hypomanic episode) was evaluated using the YMRS and the HAM-D, respectively. All patients were administered the 9-Item Patient-Rated Questionnaire (PHQ-9) (Kroenke 2001), which is shorter and widely used in primary care. All inpatients were administered following psychopathological scale at baseline (T0), after 3 (T1), 6 (T2), 12 (T3), 24 (T4) months: PHQ-9; Digit Symbol Substitution Test (DSST), designed to assess attention, psychomotor speed, and executive function (Wechsler 1981); Perceived Deficits Questionnaire 5-Item Version (PDQ) (Fehnel 2016, Sullivan 1990). All the relevant data were analysed using EZAnalyze Version 3.0, Microsoft Excel Add-In (Suffolk University in Boston, Massachusetts, USA). Chi-square test was used for analysing categorical data (age, gender, etc.). Score Data was analysed using ANOVA Test. $P<0.05$ was taken as statistically significant.

RESULTS

The patients' groups were comparable to each other in terms of age, sex, gender, SGAs, and DSM-5 episode disorders. Overall there were 11 drop outs (20%) (6 in olanzapine group; 2 in aripiprazole group; 2 in quetiapine group; 1 in asenapine group); mainly, for refusing to continue the tests (79%), other for low efficacy (12%) and for the appearance of side effects (9%) (see Table 1). Table 2 shows data of YMRS, HAM-D, and PHQ-9 scales in each group at baseline and T1, T2, T3, T4 times. The change in values at baseline and through the different periods were not significant in all pharmacological groups; these data indicate a substantial equal effectiveness of each atypical antipsychotic. However, there are little differences in HAM-D score in olanzapine and quetiapine groups (P=0.000, respectively). In

Table 3 are shown the results obtained with the DSST. The results indicate that at least two of the repeated measures differed significantly for two AAPDs. Clinically important values of statistical significance were in the aripiprazole and olanzapine groups (P=0.11 and =0.002, respectively). The asenapine and quetiapine groups showed no statistically significant difference in any time. Finally, table 4 shows the results of PDQ-5. The PDQ-5 scores were significant only in the olanzapine group (T0 vs T4: P=0.002; T1 vs T4: p=0.001, especially). There was no difference in PDQ-5 scores in the other groups. However, these data indicate that these drugs do not significantly affect cognitive ability in this group of patients.

Table 1. Demographic and other data of patients

Patient characteritics	ARZ	ASN	OLZ	QTP	
No. of cases	10	11	11	13	
Drop outs	2	1	6	2	
Age (years) mean ± SD	45.78±11.3	43.67±12.3	39.64±9.8	41.34±11.1	0.878
Gender male:female	8:2	9:2	10:1	11:2	1.403
Age of illness (ys) mean ± SD	7.2±2.1	5.41±7.2	6.3±3.8	5.9±7.7	0.342
Number hospitalizations	2.4	3.2	3.7	4.01	0.561
BD-II episodes					
depressive	2±1.54	1.545±0.68	1.364±0.809	1.385±0.962	0.012
hypomanic	0.80±0.632	1.273±0.905	1.091±0.701	1.077±0.760	0.320

ARZ - aripiprazole group; ASN - asenapine group; OLZ - olanzapine group; QTP - quetiapine group

Table 2. Data YMRD, HAM-D, PHQ-9 scales

SGAs group	Scale	T0 (mean±SD)	T1 (mean±SD)	T2 (mean±SD)	T3 (mean±SD)	T4 (mean±SD)	P value	Eta Squared	Factor A
	YMRD								
Aripiprazole		13.7±5.65	12.9±6.08	9.3±4.8	11.3±4.66	11.0±2.7	0.062	0.215	2.471
Asenapine		10.8±2.750	11.1±3.73	14±6.13	10.6±3.67	8.8±4.49	0.079	0.185	2.275
Olanzapine		11.9±3.91	12.8±5.05	10.3±4.13	11.5±4.82	13.1±3.21	0.292	0.114	1.285
Quetiapine		12.3±2.81	12.7±2.02	12.1±4.4	10.7±2.8	8.7±3.25	0.007	0.253	4.055
	HAMD								
Total		11.9±6.26	13.7±5.63	16.3±9.71	15.7±5.48	12.4±4.88	0.000	0.116	5.779
Aripiprazole		12.1±5.80	13.6±7.13	13.6±6.36	13.9±6.59	13.7±4.67	0.882	0.031	0.291
Asenapine		14.9±6.12	13.2±5.60	13.8±5.42	14.0±3.0	13.1±4.80	0.715	0.026	2.529
Olanzapine		19.5±5.41	15.6±6.04	9.2±5.11	15.6±5.73	12.8±4.84	0.000	0.403	6.764
Quetiapine		21.4±5.01	12.7±5.63	16.4±9.60	17.8±5.52	10.6±5.03	0.000	0.525	13.249
	PHQ-9								
Total		12±5.04	12.2±5.08	12.1±4.61	12.4±5.49	11.31±5.75	0.170	0.036	1.624

Table 3. Data DSST scale

SGAs group	Scale	T0 (mean±SD)	T1 (mean±SD)	T2 (mean±SD)	T3 (mean±SD)	T4 (mean±SD)	*P value*	*Eta Squared*	*Factor A*
Total		22.6±8.97	22.5±9.29	23.3±9.29	23.8±9.91	23.2±10.33	0.767	0.010	0.458
Aripiprazole		25.5±8.70	25.4±7.75	26.6±7.83	26.1±8.53	30.7±9.855	0.011	0.297	3.808
The ANOVA results indicate that at least two of the repeated measures differed significantly:									
						T0 vs T4	0.026		
						T1 vs T4	0.021		
						T3 vs T4	0.010		
Asenapine		21.2±7.27	20.54±8.58	19.3±6.66	18.2±5.08	16.2±7.28	0.090	0.178	2.173
Olanzapine		23±9.92	24.9±10.69	26.1±10.80	28.2±10.85	28.8±10.18	0.002	0.346	5.287
The ANOVA results indicate that at least two of the repeated measures differed significantly:									
						T0 vs T3	0.017		
						T0 vs T4	0.029		
						T1 vs T3	0.022		
						T1 vs T4	0.030		
Quetiapine		22.2±9.74	23.4±9.55	22.4±10.20	23.5±10.22	21±10.53	0.232	0.108	1.450

Table 4. Data DSST scale

SGAs group	Scale	T0 (mean±SD)	T1 (mean±SD)	T2 (mean±SD)	T3 (mean±SD)	T4 (mean±SD)	*P value*	*Eta Squared*	*Factor A*
	PDQ-5								
Total		11.2±4.19	10.9±4.11	10.9±3.59	10.33±4.02	10.2±4.39	0.194	0.034	1.535
Aripiprazole		11.5±5.06	11.9±4.35	11.4±3.86	10.4 ±4.9	9.1±4.09	0.097	0.192	2.135
Asenapine		10.1±3.72	10.63±4.65	11±3.46	10.91±4.50	11.36±5.626	0.738	0.047	0.497
Olanzapine		12.4±4.591	11.3±4.15	9.81±3.97	9.2 ±3.92	8.7±3.35	0.000	0.488	9.540
The ANOVA results indicate that at least two of the repeated measures differed significantly:									
						T0 vs T2	0.008		
						T0 vs T3	0.008		
						T0 vs T4	0.002		
						T1 vs T2	0.001		
						T1 vs T3	0.018		
						T1 vs T4	0.001		
Quetiapine		10.7±3.66	10±3.67	11.3±3.41	10.7±4.14	11.4±4.09	0.312	0.093	1.227

CONCLUSIONS

Cognitive impairment should be considered a critical clinical and therapeutic target, and efforts to enhance cognition may lead to higher functioning and better quality of life for patients. SGAs can be a therapeutic strategy to improve the effectiveness of treatment in BP-II. Another important aspect in these patients is the possibility to administer simple, rapid and acceptable rating scales for cognitive assessment. In our small observational study, which was not randomized and not double-blind, we observed the effectiveness of same SGAs in inpatients affected by BD-II; and their relationship to cognitive alterations. The results obtained with HAMD, YMRS and PHQ scales are similar to those obtained with the other studies, entering therefore into the normal processes of assessment and management of bipolar illness. The DSST data are rather homogeneous and show that overall SGAs do not significantly affect cognitive symptoms. However, statistical significance was observed in the aripiprazole and olanzapine groups. Some SGAs, such as quetiapine and asenapine, seem to cause a not statistically significant mild improvement.

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