ORIGINAL RESEARCH

The effect of atypical antipsychotics on brain N-acetylaspartate levels in antipsychotic-naïve first-episode patients with schizophrenia: a preliminary study

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Purpose: To investigate the correlates of a clinical therapeutic response by using the parameters measured by proton magnetic resonance spectroscopy after the administration of atypical antipsychotics.

Patients and methods: Twenty-five antipsychotic-naïve first-episode patients with schizophrenia were monitored for 12 months. The patients were evaluated using ^1H magnetic resonance spectroscopy in the dorsolateral prefrontal cortex and Positive and Negative Syndrome Scale, Clinical Global Impression Scale of Severity, Tower of London – Drexel University, Letter–Number Span Test, Trail Making Test A, and Personal and Social Performance Scale. They were administered atypical antipsychotics, starting with quetiapine. In the absence of a therapeutic response, another antipsychotic was introduced.

Results: After 12 study months, the N-acetylaspartate/creatine (NAA/Cr) level did not significantly change at the whole-group level. Additional analysis revealed a significant rise in the NAA/Cr level in the study group that stayed on the same antipsychotic throughout the study course ($P=0.008$) and a significant drop in NAA/Cr in the study group that switched antipsychotics ($P=0.005$). On the whole-group level, no significant correlations between NAA/Cr values and other scores were found at either baseline or after 12 study months.

Conclusion: One-year treatment with atypical antipsychotics administered to antipsychotic-naïve patients didn't result in a significant rise in the NAA/Cr ratio. However, a significant rise was witnessed in the study group in which a satisfactory therapeutic response had been achieved with a single antipsychotic administration.

Keywords: schizophrenia, atypical antipsychotics, NAA, MRS

Introduction

N-acetylaspartate (NAA) is considered to be the marker of neuron dysfunction and/or loss.[1–3] Akin to the level of creatine (Cr) plus phosphocreatine and some other brain metabolites, the NAA level can be determined using in vivo proton magnetic resonance spectroscopy (^1H MRS). Upon the cessation of an adverse impact or treatment, the NAA level may prove itself reversible.[4–7]

A meta-analysis that compared NAA levels in patients with schizophrenia and healthy controls found significant NAA reductions in the frontal lobe and hippocampus in patients with schizophrenia. Many authors consider that decreased NAA levels might be a biomarker for neurological diseases. The main results are presented in Table 1.[8–31] NAA changes occur in the early stage of illness. No further decrease in the NAA level was found among chronic patients.[9,10]

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Table 1 Review of previous studies

Author	Antipsychotics	Duration	Methods	Main results
Steen et al (2006)[8]	Drug naïve		Systematic review and meta-analysis	Whole brain and hippocampal volume were reduced
Fannon et al (2003)[9]	Haloperidol, olanzapine, risperidone	3 months	First-episode, ^{1}H MRS, NAA/Cr, antipsychotics at baseline and after 3 months	A significant reduction in hippocampal NAA/Cr
Bustillo et al (2008)[10]	Haloperidol, quetiapine	2 years	^{1}H MRS, frontal and occipital lobes, caudate nucleus, and cerebellum	Typical or atypical antipsychotics did not result in NAA changes
Lieberman et al (2005)[11]	Haloperidol, olanzapine	104 weeks	^{1}H MRS assessments performed at weeks 0, 12, 24, 52, and 104	Haloperidol had significant decreases in gray matter volume; olanzapine did not
Lindquist et al (2000)[12]	Haloperidol, clozapine, olanzapine	1 week	In vivo ^{1}H MRS, 4.7 T (animals)	No significant changes in NAA/Cr
Bustillo et al (2004)[13]	Haloperidol, clozapine	6 weeks	Three groups treated with antipsychotics or vehicle/6 weeks. NAA were determined by HPLC (animals)	No differences in NAA in cortex, striatum, and thalamus compared to animals treated with vehicle
Harte et al (2005)[14]	Haloperidol decanoate	24 weeks	Measured NAA in brain tissue taken from 43 males	NAA increased in the striatum
McLoughlin et al (2009)[15]	Haloperidol, clozapine, olanzapine, risperidone, aripiprazole		Metabolites were determined using ^{1}H MRS	Antipsychotics, with the exception of olanzapine, consistently increased NAA levels in at least one brain area
Bustillo et al (2006)[16]	Haloperidol decanoate	6 months	^{1}H MRS at 11.7 T in ex vivo, medial frontal and cingulate cortex, striatum, nucleus accumbens, dorsal and ventral hippocampus, amygdala, and temporal cortex (animals)	Did not result in changes in NAA, glutamate, glutamine, and other metabolites in the proton spectrum
Lindquist et al (2011)[17]	Haloperidol, clozapine	6 months	^{1}H MRS, 6 months, NAA, Cr, and Cho (animals)	Only the Cho/Cr ratio showed a significant time-by-treatment effect
Bertolino et al (2001)[18]	Clozapine, risperidone, haloperidol, fluphenazine, trifluoperazine, olanzapine, thiothixene, mesoridazine		^{1}H MRS studied twice, DLPFC	Patients on antipsychotics had significantly higher NAA measures in the DLPFC
Bustillo et al (2010)[19]	Quetiapine, risperidone, haloperidol, clozapine	12 months	^{1}H MRS of the AC, frontal white matter, and thalamus at 4 T. NAA, Glu, Gln, and Gln/Glu	NAA reductions and correlated elevations of Gln/Glu in the AC are present early in schizophrenia
Braus et al (2002)[20]	Traditional neuroleptics and atypical antipsychotics		NAA was closely correlated with perseveration errors seen on the WCST	Atypical antipsychotics modify the function of anterior cingulate neurons (improve cognitive function)
Bustillo et al (2001)[21]	Haloperidol, clozapine		Treated patients and normal controls, ^{1}H MRS of the caudate nuclei and the left frontal lobe	Exposure to haloperidol led to frontal NAA reductions previously reported in schizophrenia
Szulc et al (2007)[22]	Perphenazine, perazine, haloperidol, clozapine, olanzapine, risperidone		^{1}H MRS, voxels of 2×2×2 cm, left frontal, left temporal lobe, and left thalamus	Decrease in NAA due to typical medication may be caused by the progression of the disease, previous drug history, or by drugs

Study	Method	Findings
Yeo et al (2000)[23]	1H MRS, right frontal white matter, visual two-back test assessed working memory	Cr and NAA positively correlated with working memory skills
Valenzuela et al (2000)[24]	NAA, frontal subcortical white matter, and the occipitoparietal gray matter correlated with performance in different cognitive domains	Neurometabolic fitness of the frontal subcortical–cortical axonal fibers may be important in mediating fluid intellectual processing
Bertolino et al (2003)[25]	Subjects underwent 1H MRS and were given the N-back working memory test	Reductions of NAA in the hippocampal area and DLPFC, positive correlation between NAA in the DLPFC and performance during the two-back working memory condition
Bertolino et al (2000)[26]	1H MRS, NAA, and PET during performance of the WCST	NAA in the DLPFC strongly correlated with activation of the distributed working memory network
Tanaka et al (2006)[27]	1H MRS, left frontal lobe in 14 patients with schizophrenia and in 13 healthy comparison subjects	Decreased NAA in the left frontal lobe of patients was correlated with negative symptoms and cognitive dysfunction
Bracken et al (2013)[28]	1H MRS reporting measurements of NAA in schizophrenia with focus of methodology	Lower NAA more likely to have used longer echo times (TEs), while studies with shorter TEs reported no change
Reid et al (2013)[29]	1H MRS to quantify levels of NAA, Glu, Glx, and Cho in the left substantia nigra	No differences in levels of NAA/Cr, Glx/Cr, or Cho/Cr between the groups. Significant correlation between Glx/Cr and overall cognitive performance
Szulc et al (2013)[30]	Reviewed 27 studies, 16 before/after treatment and 11 cross-sectional about antipsychotics in schizophrenia and NAA alterations	Antipsychotics may act by increasing NAA levels in selected brain areas (frontal lobe and thalamus), especially during the short-time observation
Szulc et al (2012)[31]	PANSS, CGI, WCST, TMT, verbal fluency test, and 1H MRS were performed. Regions: left frontal, temporal, thalamus. Metabolites: NAA, Cho, myo-inositol, Glx	Correlation between WCST, negative symptoms score, education level, and myo-inositol ratio in the frontal lobe; role of the thalamus "transmission station" for psychopathology development (especially negative) in schizophrenia

Abbreviations: 1H MRS, proton magnetic resonance spectroscopy; AC, anterior cingulate; CGI, Clinical Global Impression Scale; Cho, choline; Cr, creatine; DLPFC, dorsolateral prefrontal cortex; Gln, glutamine; Glu, glutamate; Glx, glutamine plus glutamate; HPLC, high-performance liquid chromatography; NAA, N-acetylaspartate; PANSS, Positive and Negative Syndrome Scale; PET, positron emission tomography; TMT, Trail Making Test; WCST, Wisconsin Card Sorting Test; T, Tesla; N-back, N-back working memory test.

The aim of this study was to investigate the correlates of a clinical therapeutic response by using the parameters measured by ^{1}H MRS after the administration of atypical antipsychotics. The specific aim was to establish the influence of atypical antipsychotics on the NAA/Cr ratio in the dorsolateral prefrontal cortex of antipsychotic-naïve first-episode patients with schizophrenia, as well as to investigate the relationship between the NAA/Cr ratio and positive, negative, and cognitive symptoms and functioning of patients.

Materials and methods
Patients
The study enrolled patients diagnosed with schizophrenia and schizophreniform disorder in line with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria.[32] Throughout the follow-up course, all patients were expected to meet the diagnostic criteria observed with schizophrenia. Patients were recruited from the pool of consecutive outpatients seen by the Polyclinic Neuron (Zagreb, Croatia) and were all antipsychotic-naïve at the time of the first scan. All the patients had regular checkups. No psychotherapy was performed.

Exclusion criteria were: other psychiatric disorders, neurological disorders, a history of significant drug abuse, drug use in the past year, pregnancy and lactation, major somatic conditions, head trauma that rendered the patient unconscious, risk of suicide as estimated by the Columbia Suicide Severity Rating Scale,[33] and the incapacity to give informed consent. No brain atrophy or other brain morphology alteration was seen on any baseline MR imaging. Upon being thoroughly informed about the study concept, the patients gave their written informed consent. The study was approved by the institutional Board of Ethics.

Follow-up procedure
Two MR imaging scans were completed; the first one took place at baseline and the second one was scheduled for the end of the 1-year follow-up period (±1 month). Prior to each scan, the patients were administered 5–10 mg diazepam. Throughout the follow-up course, patients were administered antipsychotics in line with the study protocol. At first, quetiapine (400–800 mg QD) was introduced. In cases where a treatment response was not seen within 3 months – despite dose adjustments (as established using adequate scales), olanzapine (10–20 mg QD) was introduced. In cases where the above history repeated itself, olanzapine was first replaced by risperidone (2–8 mg QD) and then by clozapine (100–900 mg QD).

The study was initially comprised of 30 patients. Two of them were subsequently excluded after they had an overwhelming fear response that prevented the completion of either the first or second scan. One examinee withdrew his informed consent, while one witnessed a major deterioration and had to be hospitalized, rendering him unable to complete the study. Following the first scan, one examinee suffered an injury to his eye caused by metal foreign body penetration. This injury necessitated his departure from the study. The study was completed by 25 examinees. Upon the study's completion, ten patients were treated with quetiapine, ten with olanzapine, and four with risperidone, while clozapine was not taken by any of the patients. Despite the study's protocol, in the single case where a patient developed metabolic syndrome, ziprasidone had to be introduced.

Instruments
Both at baseline and at every 3 months for the remainder of the study, the following tests were administered: Positive and Negative Syndrome Scale (PANSS)[34] applicable for psychopathology, Clinical Global Impression of Severity (CGI-S)[35] suitable for the determination of severity level, Tower of London – Drexel University (TOL DX),[36] Trail Making Test A (TMT-A)[37] and Letter–Number Span Test (LN)[38] suitable for swift neuropsychological assessment, and Personal and Social Performance Scale (PSP)[39] suitable for the determination of functionality level.

PANSS consists of positive, negative, and general psychopathology scales. For TOL DX, which is viewed as the executive functions test, the examinee is required to move several differently colored beads across three pegs in line with a predestined pattern, making as few moves as possible. Within the frame of TMT-A, which is viewed as the visual attention test, the examinee is asked to connect randomly arranged numbers in their sequential order. LN, which is considered to be a working memory test, requires the examinee to sort relatively short sequences of randomly presented letters and numbers in both sequential and alphabetic order.

Treatment response was evaluated using CGI-S and CGI of Improvement[35] every 3 months. In addition, the Simpson–Angus Scale[40] for parkinsonism, Abnormal Involuntary Movements Scale[41] for tardive dyskinesia, and the Barnes Akathisia Rating Scale[42] for akathisia were used every 3 months.

^{1}H MRS
Patients were scanned using a 3T MR device (Magnetom® Trio; Siemens AG, Erlangen, Germany) equipped with a 12-channel head coil suitable for MRS. Standard T1 and

T2 sequences completed in the coronal, sagittal, and axial plane and covering the entire brain were acquired for each subject to the effect of spectral localization and exclusion of possible structural brain damage. The spectroscopic volume of interest, having a size of 15×15×15 mm, was selected in the left dorsolateral prefrontal cortex region (Figure 1) so as to minimize the amount of cerebrospinal fluid contained in the volume of interest.

Given the fact that the patients' profiles called for shorter scanning times, the left dorsolateral prefrontal cortex, which is the brain area frequently targeted by other authors as well, was focused on. Single-voxel spectra were acquired using a point-resolved spectroscopy; the echo time equaled 135 milliseconds, with a repetition time of 2,000 milliseconds and a spectral width of 10 ppm. The target area was scanned 128 times on average with a scanning time of 4:17 minutes. An appropriate automated procedure was used to optimize field homogeneity, radiofrequency pulse power, and water suppression, as well as to convert the lines into a Gaussian shape. A typical ^{1}H MRS spectrum is shown in Figure 1. By virtue of the foregoing, integral values of NAA and Cr peaks were obtained, while NAA/Cr ratios were used for further analysis.

Statistical analysis

The Smirnov–Kolmogorov test was used to analyze data distribution. Due to the nature of the findings and a relatively small sample size, nonparametric tests were employed with other analyses. Medians and corresponding interquartile ranges were used to describe quantitative values. Differences in antipsychotic drug use and quantitative scores (PANSS, CGI-S, TOL DX, LN, TMT-A, and PSP scores and NAA/Cr values) seen between the study groups, were analyzed using the Mann–Whitney U test. The Wilcoxon test was used to assess differences between quantitative variables seen at the beginning and at the end of the study (after 12 months). Spearman's correlation coefficients (rho) were calculated so as to analyze the

correlation between MR findings and test scores. All P-values lower than 0.05 were considered statistically significant. All statistical analyses made use of IBM SPSS® Statistics version 19.0.0.1 (IBM Corporation, Armonk, NY, USA).

Results

Twenty-five patients were monitored for 12 months: 15 (60.0%) had used more than one antipsychotic drug. The majority of patients were men (20; 80.0%). The educational background of the study group was as follows: 16 examinees (64.0%) had 12 years of formal education. Thirteen patients (52.0%) were unemployed, 17 (68.0%) were single, and 18 (72.0%) declared themselves tobacco smokers. All patients were right-handed.

Viewed on the whole-group level, no significant NAA/Cr changes were seen after 12 months of study (P=0.668). The subsequent analysis embraced two distinctive patient groups: one included patients who – due to their favorable and swift therapeutic response – remained on initial quetiapine therapy throughout the study course, and the other included patients who, within the same timeframe, had to be administered two or more atypical antipsychotics. There were no significant differences between the groups (Table 2). It is possible that the first group maintained better therapy compliance or social support. Throughout the monitoring period, these two groups showed no significant differences in their scores on the following psychiatric tests: PANSS, CGI-S, TOL DX, LN, TMT-A, and PSP. The only exception was the NAA/Cr ratio after 12 months, which was significantly higher in the group that stayed on the same antipsychotic drug throughout the study course (median [IQR] 1.93 [1.87–2.27]) compared to the drug-changing group (1.70 [1.37–1.77]; P=0.006). As for the differences between paired measures (baseline versus month 12), the drug-changing group exhibited noteworthy dynamics: total PANSS score (P=0.001), positive PANSS score (P=0.001), general PANSS score (P=0.011), CGI-S score (P=0.018),

Table 2 Sociodemographic characteristics of the two investigated groups

	More than one antipsychotic N=15					One antipsychotic N=10					P-value
	Mean	SD	Percentiles			Mean	SD	Percentiles			
			25th	50th (median)	75th			25th	50th (median)	75th	
Age, years	25.00	3.25	22.00	25.00	28.00	26.10	3.00	23.00	26.00	29.00	0.402
Education, years	11.93	0.70	12.00	12.00	12.00	12.80	1.87	11.75	12.00	14.50	0.330
Duration of disease, months	23.73	14.71	11.00	21.00	38.00	24.90	7.50	18.75	24.00	27.50	0.560
Male sex: n (%)*	12 (80%)					8 (80%)					0.610

Note: *$P<0.05$.
Abbreviations: SD, standard deviation; N, number of patients.

Table 3 Differences in measured values found across the group taking more than one antipsychotic drug (N=15) – Wilcoxon test

	Minimum	Maximum	25th percentile	Median	75th percentile
PANSS positive 0*	12.00	28.00	13.00	17.00	19.00
PANSS positive 12*	8.00	15.00	10.00	11.00	13.00
PANSS negative 0	12.00	31.00	20.00	21.00	26.00
PANSS negative 12	16.00	27.00	17.00	21.00	22.00
PANSS general 0*	28.00	55.00	30.00	33.00	37.00
PANSS general 12*	23.00	34.00	28.00	31.00	33.00
PANSS total 0*	59.00	114.00	65.00	72.00	81.00
PANSS total 12*	49.00	75.00	57.00	62.00	69.00
CGI-S 0*	3.00	5.00	3.00	4.00	5.00
CGI-S 12*	1.00	4.00	2.00	2.00	3.00
TOL DX 0	15.00	65.00	30.00	34.00	53.00
TOL DX 12	4.00	84.00	27.00	35.00	55.00
LN 0*	9.00	15.00	11.00	12.00	13.00
LN 12*	13.00	22.00	18.00	19.00	22.00
TMT-A 0	28.00	111.00	41.00	64.00	76.00
TMT-A 12	34.00	85.00	45.00	51.00	61.00
PSP 0*	45.00	80.00	55.00	60.00	70.00
PSP 12*	63.00	84.00	68.00	73.00	76.00
NAA/Cr 0*	1.280	2.690	1.570	1.850	2.010
NAA/Cr 12*	1.240	2.710	1.370	1.700	1.770

Note: *$P<0.05$.
Abbreviations: CGI-S, Clinical Global Impression of Severity; Cr, creatinine; LN, Letter–Number Span Test; NAA, N-acetylaspartate; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale; TMT-A, Trail Making Test A; TOL DX, Tower of London – Drexel University.

and NAA/Cr ($P=0.008$) decreased, while LN score ($P=0.001$) and PSP score ($P=0.001$) increased (Table 3). In the group that stayed on the same antipsychotic drug throughout the study course, total PANSS score ($P=0.032$), positive PANSS score ($P=0.009$), negative PANSS score ($P=0.027$), and CGI-S score ($P=0.025$) decreased, while LN score ($P=0.005$), PSP score ($P=0.008$), and NAA/Cr ($P=0.005$) increased (Table 4).

Table 4 Differences in measured values found across the group sticking to the same antipsychotic drug throughout the study course (N=10) – Wilcoxon test

	Minimum	Maximum	25th percentile	Median	75th percentile
PANSS positive 0*	13.00	21.00	15.25	16.50	18.25
PANSS positive 12*	7.00	17.00	8.50	10.00	13.00
PANSS negative 0*	17.00	29.00	20.00	23.50	25.50
PANSS negative 12*	16.00	27.00	17.00	21.00	22.25
PANSS general 0	27.00	44.00	29.00	33.50	40.50
PANSS general 12	24.00	42.00	28.75	30.50	33.50
PANSS total 0*	60.00	85.00	64.00	77.00	83.00
PANSS total 12*	53.00	80.00	54.00	62.00	67.00
CGI-S 0*	3.00	5.00	3.00	4.00	5.00
CGI-S 12*	1.00	4.00	2.00	3.00	3.00
TOL DX 0	23.00	55.00	30.00	41.50	49.00
TOL DX 12	7.00	78.00	15.00	24.50	58.00
LN 0*	4.00	17.00	8.00	10.00	12.00
LN 12*	15.00	21.00	17.00	18.50	19.00
TMT-A 0	38.00	109.00	44.00	66.00	83.00
TMT-A 12	37.00	81.00	43.00	51.00	72.00
PSP 0*	45.00	65.00	51.00	54.00	65.00
PSP 12*	57.00	78.00	64.00	70.50	75.00
NAA/Cr 0*	1.360	2.100	1.620	1.685	1.820
NAA/Cr 12*	1.640	2.590	1.880	1.925	2.180

Note: *$P<0.05$.
Abbreviations: CGI-S, Clinical Global Impression of Severity; Cr, creatinine; LN, Letter–Number Span Test; NAA, N-acetylaspartate; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale; TMT-A, Trail Making Test A; TOL DX, Tower of London – Drexel University.

In the group with more than one antipsychotic drug, significant negative correlations of NAA/Cr with PANSS positive and TOL DX score were found at the beginning of the study. After 12 months, NAA/Cr levels were significantly positive correlated with Hamilton Depression Rating Scale and LN scores.

At the beginning of the study in the group with only one antipsychotic drug, a significant correlation was noted between NAA/Cr and Hamilton Depression Rating Scale levels. After 12 months, significant and strong negative correlations of NAA/Cr with CGI-S and TMT-A scores were found (Table 5).

Viewed on the whole-sample level, no significant correlations between NAA/Cr values and other scores were seen either at baseline or after 12 study months. The same goes for the baseline status of the patients changing their antipsychotic drugs in the further course. After 12 study months, significant correlations between NAA/Cr and other scores were noted only among drug-switching patients, in whom a positive correlation with LN score was established (rho=0.617; *P*=0.014).

Discussion

This study failed to demonstrate any significant difference in NAA/Cr throughout the administration of the novel antipsychotic drug. Similar results were obtained in several recent studies.[10,19] However, an intra-sample comparison of patients who favorably and swiftly responded to initial therapy with patients who needed two or more antipsychotic drugs (in order to attain a satisfactory therapeutic response) pointed towards different outcomes. Upon completion of the therapy, the first patient group showed a significant rise in NAA/Cr, both from baseline and compared to the second patient group's month 12 results. The second patient group not only failed to experience a rise in NAA/Cr, but also experienced a drop in NAA/Cr throughout the therapy course, despite the satisfactory end-study stage therapeutic response (Figure 2).

To the best of the authors' knowledge, this is the very first follow-up study carried out in antipsychotic-naïve first-episode schizophrenic patients. The baseline scan was performed without any antipsychotic or other treatment except 5–10 mg diazepam for all patients. The differing
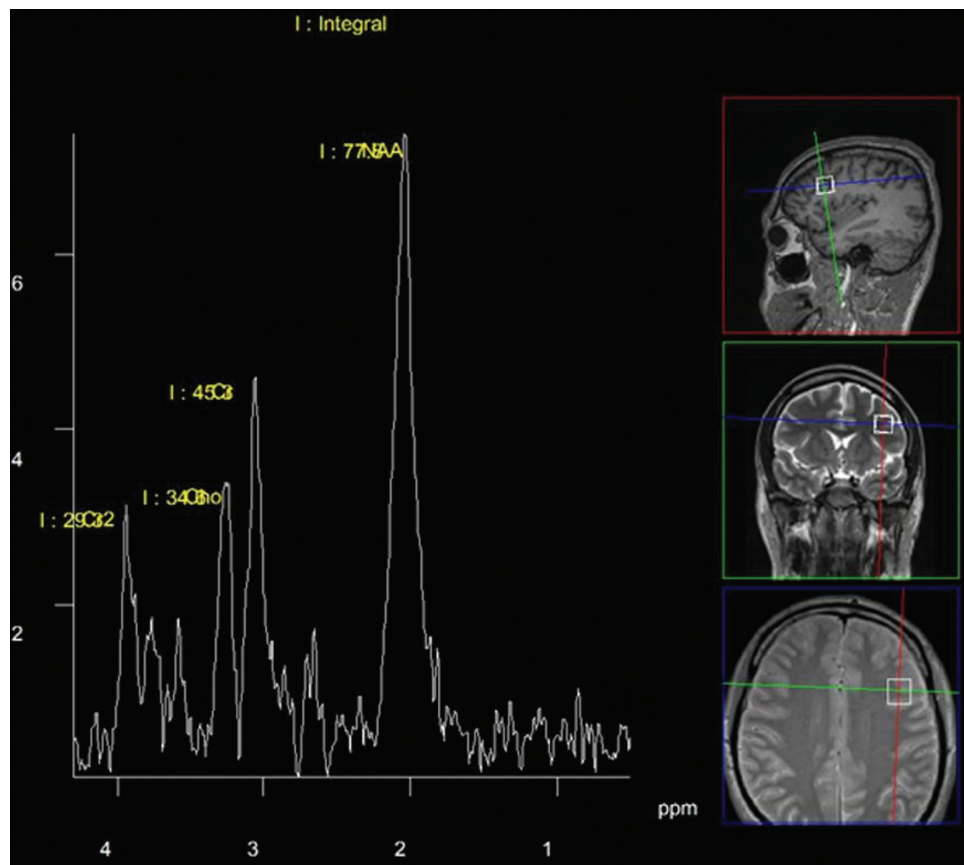

Figure 1 A typical ¹H spectrum and the spectroscopic volume of interest: left dorsolateral prefrontal cortical region.
Note: Image from an outpatient of Polyclinic Neuron, Croatian Institute for Brain Research (Zagreb, Croatia).

Table 5 Spearman's correlation coefficients (rho) between functional outcome and NAA/Cr level at the beginning of the study and after 12 months

		More than one antipsychotic N=15		One antipsychotic N=10	
		0 NAA/Cr	12 NAA/Cr	0 NAA/Cr	12 NAA/Cr
PANSS positive 0	rho	0.032	0.327	−0.414	−0.549
	P-value	0.908	0.234	0.235	0.100
PANSS negative 0	rho	0.081	0.263	−0.079	−0.341
	P-value	0.774	0.343	0.828	0.334
PANSS general 0	rho	−0.110	−0.017	0.188	−0.316
	P-value	0.696	0.952	0.602	0.374
PANSS total 0	rho	0.105	0.288	0.079	−0.394
	P-value	0.708	0.298	0.829	0.260
HAM-D 0	rho	0.229	0.015	0.748	0.056
	P-value	0.412	0.958	0.013	0.878
SAS 0	rho	0.193	0.025	0.108	0.362
	P-value	0.491	0.929	0.766	0.304
CGI-S 0	rho	−0.040	0.104	−0.360	−0.809
	P-value	0.888	0.713	0.307	0.005
TOL DX 0	rho	−0.509	−0.195	0.207	0.286
	P-value	0.053	0.485	0.567	0.424
LN 0	rho	−0.112	−0.068	−0.171	0.250
	P-value	0.692	0.810	0.637	0.486
TMT-A 0	rho	−0.179	0.159	−0.418	−0.673
	P-value	0.524	0.571	0.229	0.033
PSP 0	rho	−0.169	−0.337	0.148	0.412
	P-value	0.547	0.219	0.684	0.236
PANSS positive 12	rho	−0.522	−0.422	0.233	−0.098
	P-value	0.046	0.118	0.517	0.787
PANSS negative 12	rho	−0.250	−0.180	0.068	−0.006
	P-value	0.368	0.520	0.853	0.987
PANSS general 12	rho	−0.392	−0.146	0.091	0.006
	P-value	0.148	0.602	0.802	0.987
PANSS total 12	rho	−0.411	−0.202	0.245	−0.043
	P-value	0.128	0.470	0.496	0.907
HAM-D 12	rho	0.113	0.598	0.443	0.117
	P-value	0.687	0.019	0.200	0.748
SAS 12	rho	−0.148	−0.062	−0.007	0.052
	P-value	0.600	0.825	0.984	0.886
CGI-S 12	rho	0.200	0.108	0.658	−0.111
	P-value	0.474	0.702	0.039	0.761
CGI-I 12	rho	0.080	0.068	0.623	−0.159
	P-value	0.776	0.810	0.054	0.661
TOL DX 12	rho	−0.586	−0.265	0.248	0.188
	P-value	0.022	0.341	0.489	0.603
LN 12	rho	0.385	0.617	0.228	0.426
	P-value	0.156	0.014	0.526	0.220
TMT-A 12	rho	−0.497	−0.023	−0.012	−0.480
	P-value	0.059	0.934	0.973	0.160
PSP 12	rho	0.136	0.020	−0.134	0.146
	P-value	0.628	0.944	0.713	0.688

Abbreviations: CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression of Severity; Cr, creatinine; HAM-D, Hamilton Depression Rating Scale; LN, Letter–Number Span Test; NAA, N-acetylaspartate; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale; SAS, Simpson–Angus Scale; TOL DX, Tower of London – Drexel University; TMT-A, Trail Making Test A.
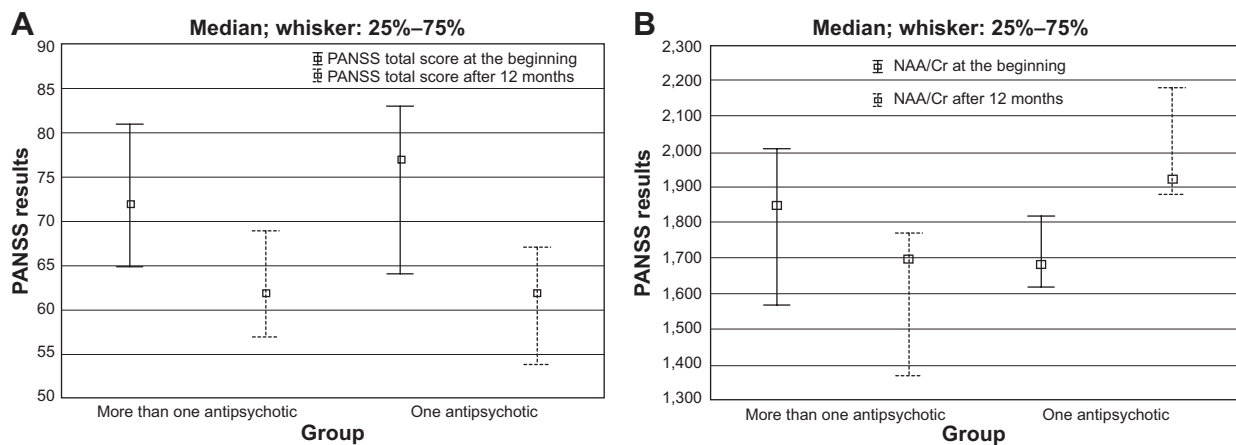
Figure 2 Comparison of NAA/Cr levels between two groups that had more than one antipsychotic, or had one antipsychotic.
Notes: (**A**) Both groups showed improvement in total PANSS score. (**B**) In the drug-changing group, the NAA/Cr ratio decreased; however, in the group sticking to the same antipsychotic drug, the NAA/Cr ratio increased after 12 months.
Abbreviations: Cr, creatinine; NAA, N-acetylaspartate; PANSS, Positive and Negative Syndrome Scale.

results of the two groups might explain why the outcomes of previous studies vary to such a great extent. Differences in study outcomes could also be attributed to the differences in duration of the monitoring period, as well as the differences in sample sizes, selection of the target brain region, and the employed ^{1}H MRS technique. In addition, the administered antipsychotic drugs were mutually different and given in various disease and treatment stages. The authors are fully aware of the limitations of this study, which can be attributed to the size of the studied sample. This was especially apparent with the intra-sample patient grouping; however, the fact that the patients who stayed on a single antipsychotic drug throughout the monitoring period exhibited a unanimous rise in NAA/Cr levels deserves attention and should be considered indicative.

The current results correspond with those of another study which demonstrated a drop in NAA levels across the non-remitting patients and a rise in NAA levels across the remitting patients, even though a 28-day treatment of manic adolescents failed to yield any rise in total NAA levels.[43] It is worth noting that the patients treated within the framework of the above study received olanzapine, which failed to yield a rise in NAA levels in the examinees (N=10) despite the achieved therapeutic response. That could be best explained by the fact that this study focused on patients with schizophrenia, while the study in reference was comprised of type I bipolar disorder patients. The results could also be related to the affective basis of bipolar disorder.[44] In addition, the NAA rise witnessed within the framework of the latter study is more likely to be attributed to the alleviation of manic symptoms than to the olanzapine-related therapeutic effects. Even though the patients in the current study were treated with

more than one atypical antipsychotic drug and unanimously responded to treatment (thereby taking the study design into account), the rise in NAA/Cr levels was witnessed only in the quetiapine monotherapy arm. Such a finding, together with the lack of olanzapine-related therapeutic benefits, could be suggestive of differences in the acting mechanisms of various atypical antipsychotic drugs, at least when it comes to NAA. Pending additional research, of course, MRS might prove to be a useful guide for choosing the early-stage therapy of patients with schizophrenia. However, the fact that olanzapine was the first administered and the last withdrawn drug in the study protocol – that is to say, the only drug administered to the study group throughout the entire 12-month study course – should not be neglected.

This study failed to reveal any substantial relationship between NAA/Cr and a psychopathology profile. The correlation between the investigated variable and cognitive functioning is merely suggested by the positive correlation with LN scores, which was seen only at follow-up month 12 and only in patients taking more than one antipsychotic drug. The absence of correlation between the investigated parameter and cognitive functioning could be attributed in part to a lower number of employed tests compared to some of the previous studies. That is, within the frame of the current study, only rapid neuropsychological testing was carried out, mostly because of the patients' profiles; on the occasion of the first testing, the patients were acute and antipsychotic medication-naïve.

While some of the studies from the introduction managed to demonstrate a correlation between the alterations in ^{1}H MRS – established metabolite concentrations and various symptoms (only in functionally-related brain regions,

however), other studies failed to reveal such a specific pattern and operated on the presumption of wider white and gray matter damage inflicted by schizophrenia.[45] Bustillo et al are of the opinion that studies investigating schizophrenia, which implies minor, albeit widespread, white and gray matter alterations, should aim to target wider brain regions.[46]

This is also a limitation of the current study, which targeted one brain region only. Another limitation may be the sole availability of baseline and final MR scans. Additional scans would significantly contribute to a better understanding of NAA/Cr study dynamics, especially when it comes to scores obtained with the employed battery of tests.[47]

Conclusion

In summary, a 1-year administration of atypical antipsychotic drugs to antipsychotic-naïve patients failed to evoke any substantial rise in NAA/Cr. However, a significant increase in NAA/Cr levels was seen in patients who stayed on their initial antipsychotic medication, which yielded a favorable therapeutic response. Despite the limitations of the current study, this finding points towards a link between NAA/Cr levels and atypical antipsychotic medication, which should be further investigated within a broader framework.[48]

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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