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ORIGINAL PAPER

Cognitive Efficacy of Quetiapine in Early-Onset First-Episode Psychosis: A 12-Week Open Label Trial

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Abstract Twenty-three adolescents with psychotic disorders, aged from 13 to 18 years, participated in a 12-week open label trial (17 adolescents completed the study) in order to examine the impact of quetiapine on clinical status and cognitive functions (encompassing processing speed, attention, short-term memory, long-term memory and executive function). An improvement in Clinical Global Impression and Positive and Negative Symptom Scale (P's ≤ 0.001) was observed. In addition, after controlling for amelioration of symptoms, a significant improvement was observed on one executive function ($P = 0.044$; Trail Making Part B). The remaining cognitive abilities showed stability. In addition, we observed an interaction between quetiapine doses (>300 mg/day or <300 mg/day) and time, where lower doses showed more improvement in verbal short-term memory ($P = 0.048$), inhibition abilities ($P = 0.038$) and positive symptoms ($P = 0.020$). The neuropsychological functioning of adolescents with psychotic disorders remained mainly

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stable after 12 weeks of treatment with quetiapine. However, lower doses seemed to have a better impact on two components of cognition (inhibition abilities and verbal short-term memory) and on positive symptoms.

Keywords Schizophrenia · Psychosis · Adolescence · Cognition · Neuropsychology · Quetiapine · Antipsychotic treatment · Cognitive enhancer

Introduction

Psychotic disorders comprise a wide spectrum of disabilities ranging from positive (hallucinations, delusions) and negative (alogia, anhedonia, avolition, flat affect) symptoms [1] to cognitive impairments in attention, processing speed, working memory, long-term verbal memory and executive functions [2–6]. These cognitive deficits are related to poorer functional outcome [7, 8]. More specifically in adolescents with psychotic disorders, these cognitive disabilities interfered with a period of important educational, social and emotional development [9]. Therefore adolescents suffering from psychotic disorders are a major concern for clinicians or mental health institutions having to find the most optimal treatments alleviating symptoms as well as being well adapted and self satisfactory for this age group.

Atypical antipsychotics (e.g. olanzapine, risperidone, quetiapine) have shown good tolerability and proven to be effective in treating negative and positive symptoms as well as promising improvement on cognitive impairment in adults with schizophrenia [10–14]. In adolescents with psychotic disorders, the efficacy of atypical antipsychotics on positive and negative symptoms has also been proven in different studies [15–19]. More specifically, in this population, quetiapine has been shown to reduce symptoms, to be well tolerated and to be associated with low weight gain and low extra-pyramidal symptoms occurrence [17, 20–22]. Atypical antipsychotics share some pharmacological properties in that almost all of them are antagonists at dopaminergic D_2- and serotonergic 5-HT_{2a} receptors, in relationship with their effects on positive symptoms and negative symptoms, respectively [23]. Quetiapine shares structurally some common properties with the antipsychotic drug loxapine, which is metabolized by N-demethylation to the antidepressant drug amoxapine [24]. Quetiapine is one of the atypical antipsychotic drugs also introduced for the treatment of bipolar depression and as that, it is considered to be a first line option in international guidelines [25]. Interestingly, quetiapine similarly to loxapine is also demethylated: its metabolite norquetiapine [24] is a potent norepinephrine reuptake inhibitor and a partial 5-HT_{1a} agonist. Serotonin and noradrenaline are implicated in cognitive mechanisms [26, 27]. To the best of our knowledge, only one comparative, randomized, single-blind, 6-month study explored cognitive improvement related to treatment by quetiapine compared to olanzapine in an adolescent population [9]. Results revealed no amelioration in attention, working memory, learning and memory or executive functions. Therefore, further clinical trials are needed in order to replicate and confirm these results.

Thus, the present clinical study aimed at measuring the impact of quetiapine on cognitive functions and clinical status in adolescents with psychotic disorders. The impact of quetiapine on cognitive functions was assessed by neuropsychological tests before and after 12 weeks of quetiapine treatment. This investigation is part of a study on the clinical effectiveness and tolerability of quetiapine in adolescents with non-affective psychotic disorders [28].

Methods

Study Design

The comprehensive design of this study as it was presented in details elsewhere [28] is summarized as follows: this was a two-site (Lausanne and Bern university hospitals) open-label trial in adolescents with psychotic disorders, in which assessments of cognitive impact and clinical efficacy of quetiapine were performed over 12 weeks. The study was approved by the Ethical Committee of the Lausanne University Hospital. Written informed consent was obtained prior to any study procedures by all patients and parents or legal representatives as required. Treatment discontinuation and study withdrawal could be motivated at any time by the subjects or the investigators.

Inclusion Criteria

Adolescents (13–18 years old) who fulfilled the DSM IV criteria for schizophrenia (295.10, 295.20, 295.30, 295.60, 295.90), schizophreniform disorder (295.40), schizo-affective disorder (295.70), delusional disorder (297.1), brief psychotic disorder (298.8), substance-induced psychotic disorder (293.xx), psychotic disorder NOS (298.8), mood disorders with psychotic features (296.x4) and who had no current medication or for whom initial antipsychotic treatment showed lack of efficacy or poor tolerance were targeted.

Exclusion Criteria

Subjects were excluded from the study if they showed (1) evidence of substance abuse (positive urine screening to opiates or ecstasy). Some cannabis consumption was not considered as exclusion criteria as this behavior is frequent in this population, for which effective treatments are needed; (2) a history or present condition of organic mental disorders, (3) mental retardation (IQ < 70, defined as need for special education, assessed through a screening of the medical records about the activities before the first psychotic episode), (4) clinically meaningful non stable cardiovascular, (5) hepatic or renal diseases, (6) leucopenia (WBC $< 4{,}000/mm^3$) or (7) pregnancy, or if they were currently enrolled in another medical trial.

Patients

A total of 23 participants were screened and selected in the study, 17 from center one (Lausanne) and 6 from center two (Berne). The adolescents were aged between 13 and 18 years (Mean $\pm$ SD: 15.8 $\pm$ 1.38 years), 17 of them were male (6 females) and 20 were Caucasian. DSM-IV diagnoses included schizophrenia (7), schizophreniform disorder (6), schizoaffective disorder (1), psychotic disorder not otherwise specified (6), delusional disorder (2) and brief psychotic disorder (1). All 23 subjects received quetiapine, 17 completed the treatment (Completer) and 6 discontinued early (Non-completer) due to consent withdrawal (3), lack of compliance (1), lack of efficacy (1) and the occurrence of a serious adverse event (1).

Psychiatric comorbidities were present in the medical history of 11 patients: Eating disorder (1 patient), obsessive compulsive disorder (1), sexual abuse by an adult (1), substance abuse (1), suicide attempts (1), conduct disorder (2), depression and self-injuries (1),

depression (1), onset psychosis as a child (1), social anxiety (1). 14 patients presented other than psychiatric problems in their medical history: Dermatological pathologies (5), musculoskeletal system (4), endocrinological system (3) (including 2 patients with hyperprolactinemia), peripheral nervous system (2), respiratory system (2), gastro-intestinal tract (1), cardiovascular system (1), blood (1) and allergy (1).

Premedications and Concomitant Medications

Concomitant medications were given only if considered necessary for the participants' safety or well-being. A failure of previous ongoing antipsychotic treatments lead to enrolment in the present study and so was discontinued. Eight participants received antipsychotic medication before the start of the quetiapine treatment: only olanzapine (3); only risperidone (3); olanzapine and risperidone (1); olanzapine, levomepromazine and zuclopenthixol (1). A wash-out period of at least 24 h was observed for any participant receiving prior antipsychotic treatments. In addition, for drug-naïve patients, a short period of treatment with the benzodiazepines clorazepate, alprazolam or diazepam could be conducted if needed.

Hepatic enzyme-inducing agents (e.g. carbamazepine, barbiturates, glucocorticoids) had to be avoided as concomitant medication. No other psychotropic medication was allowed except alprazolam, diazepam, clorazepate in case of severe agitation, chloral hydrate in case of invalidant insomnia, biperidene when appropriate.

Medication Dosing

Doses were adjusted by senior psychiatrists of both sites (L.H. and U.P.) in function of efficacy and tolerability in order to improve the compliance and to limit side effects (as sedation, for example). Quetiapine doses (computed by summing the total amount of administered doses divided by the number of days of exposure) ranged between 42 and 858 mg, the mean daily dose was 350 ± 213 mg/days. Mean exposure time to quetiapine was 77 ± 28 days, with a minimum of 9 and a maximum of 106 days of exposure. Plasma concentrations of quetiapine as assayed by a previously described method [28] were 213 ± 277 ng/ml at week 12 ($n = 14$). As about half of the patients received doses lower than 300 mg/day, in the final part of the analyses the adolescents were split in function of the received doses (>300 mg/day or <300 mg/day) in order to explore for possible differences of the effect of quetiapine doses on cognition and clinical status. The mean doses for the "low doses group" ($n = 8$) were 136 ± 82 mg/day (range 42–273 mg/day) and of 498 ± 130 mg/day (range 339–858 mg/day) for the "high doses group" ($n = 9$). Plasma levels of quetiapine confirmed the repartition of the adolescents (at week 12 it was of 14 ± 9 ng/ml and of 363 ± 287 ng/ml for the lower and higher doses group, respectively) in that, as expected, plasma levels of quetiapine were lower in the low dose than in the high dose group.

Assessments

Clinical Status

Participants were assessed with the Positive and Negative Symptom Scale (PANSS), assessing positive and negative symptoms as well as general psychopathology in subjects

with schizophrenia and related disorders [29]. Clinical efficacy was evaluated with the Clinical Global Impression-Severity of illness scale (CGI) [30]. Evaluations were conducted both at baseline and at study week 12.

Neurocognitive Test Battery

A comprehensive test battery was administered by a trained neuropsychologist at baseline and after 12 weeks of treatment. The psychometric tests were chosen because they represent main functions which can be altered in psychotic disorder, i.e. processing speed, attentional abilities, memory abilities and executive function [2, 5, 6].

Processing speed ability was assessed with the Trail Making Test—Part A [31] where digits ranging from 1 to 25 had to be connected with a continuous line. In addition, the part of the Stroop task, where images were to be named, was also used to assess processing speed abilities. The time to realize the tests were recorded.

Selective and Sustained Attention were assessed with the Continuous Performance Test (CPT) degraded version [32, 33]. In this test, stimuli were presented to the participant who had to detect (by pressing on a key response) the occurrence of a target stimulus during an 8-min period. The scores were the hit rate (mean success rate), the false alarm rate (responding to interfering stimuli), d' (computed from the proportion of hits and false alarms) representing a measure of signal/noise discrimination (i.e. the ability to discriminate between target and non-target).

Short term memory ability was assessed with two tests. Firstly, the Audio Span Test [34] was administered. In this task, clusters of numbers were read by the examiner and had to be repeated by the participant. Secondly, in the Visuo-spatial Span Test [35] visuo-spatial sequences were performed by the examiner and repeated by the subject in the same order. The scores were made of the maximal cluster of numbers or the maximal visuo-spatial sequence correctly repeated.

Long term memory ability was assessed with two tests. Firstly, the Rey Auditory Verbal Learning Test [36] which consisted in a list of 15 words that the participant had to learn through 5 immediate recall. Then, a delayed recall was required. The score used for this task was the number of words correctly recalled in the delay recall. Secondly, the complex figure of Rey [37] was used. This task consisted in copying and recalling a complex geometrical figure. The score was made out of the correct recall of the elements of the geometrical figure.

Executive functions were assessed with three tests. First, in the Verbal Fluency Task [38] as many words as possible of one category (letter M or animal) had to be generated in a limited time (60 s). The score was made of the total number of correct words expressed in both part (with the letter M and animal). Secondly, the Trail Making Test—Part B [31] was administered. In this task, participants had to connect digits and numbers alternatively. The time to realize this task and errors were recorded. The interference condition of the Stroop task requires suppressing the automatic response of word learning in favor of the less automatic process of object naming. Speed of naming (time score) and the number of interference errors were recorded.

Additional Measures

Urine sample was asked for illicit drug detection at week 0. Semi-quantitative urine analyses included the following substances: cannabis, benzodiazepines, opiates, cocaine, methadone and amphetamines. In addition, the substance use and frequency before and

during the study were assessed by the substance use questionnaire derived from the Adolescent Drug Abuse Diagnosis [39]. Thus, at baseline, one participant injected heroin, and eight patients drunk alcohol 1–5 times during the past month (usually 1–6 drinks per day). Eleven participants smoked every day tobacco during the past 6–48 months. In addition, 10 participants smoked regularly [several times per week ($n = 5$) or per day ($n = 5$)] cannabis during the past 12–48 months. Two participants had to be considered as polydrug users, as they reported to drink alcohol and smoke cannabis and tobacco, as well as to intake amphetamines, tranquilizers, cocaine, hallucinogens and phencyclidine.

Statistical Analysis

Descriptive statistics were provided for dependant variables. Everywhere, if not otherwise mentioned, data were presented as means ± SD. As the data suit a Gaussian distribution, parametric tests were used. First, we tested the effect of antipsychotic pre-medication using independent tests of Student on the evaluation at baseline and at the end of the study. Then dependent sample tests of Student assessed the changes in performance on neuropsychological tests. After testing for main effect of quetiapine on cognition, analyses of covariance (with the amelioration of the symptoms as covariate) were computed [40]. Then, correlation analyses were conducted between changes in clinical status and changes in cognitive abilities. After that, 2 (quetiapine doses: higher or lower than 300 mg/day) × 2 (time: Baseline vs. at week 12) analyses of variance (ANOVA) were conducted in order to observe possible interaction effects between time and quetiapine doses. Finally, differences between patients who did (completer) and did not complete (non-completer) the study were assessed with independent sample tests of Student at baseline.

Results

Pre-Medication Effect

The effect of previous antipsychotic medication was tested at baseline and at the end of the study. Results revealed no significant differences on clinical status, cognitive abilities or rate of non completers between the participants who take antipsychotic medication prior to the study versus the participants who did not receive any antipsychotic before the study.

Impact of Quetiapine on the Clinical Status

At the end of the study, significant reduction was observed on the three subscales of the PANSS (positive, $P < 0.001$; negative, $P = 0.004$; general psychopathology subscales, $P < 0.001$). In addition, the severity of the symptoms decreased during the 12 weeks treatment ($P < 0.001$), (Table 1).

Impact of Quetiapine on Cognition

Changes on neuropsychological testing are displayed in Table 2. A statistically significant improvement in processing speed was found regarding the denomination part (picture naming) of the Stroop task ($P = 0.002$) and the Part A of the Trail Making Test task showed marginal differences ($P = 0.065$). However, after controlling for the amelioration

Table 1 Descriptive scores for the symptomatology

Scale	*N*	Baseline	At week 12	Changes from baseline to week 12		
		Mean (SD)	Mean (SD)	Mean (SD)	*t*	*P*
CGI Severity	20	4.90 (0.64)	3.35 (0.99)	1.55 (1.00)	6.94	<0.001
PANSS Positive	20	22.60 (5.74)	16.85 (6.85)	5.75 (5.25)	4.90	<0.001
PANSS Negative	20	26.20 (5.99)	21.25 (5.43)	4.95 (5.72)	3.87	0.001
PANSS Global	20	48.30 (7.98)	37.55 (9.23)	10.75 (10.23)	4.70	<0.001

Mean scores on Clinical Global Impression-Severity of illness scale (CGI Severity) and on the general psychopathology (PANSS Global), negative symptoms (PANSS Negative) and positive symptoms (PANSS Positive) subscales of the PANSS: at baseline, at week 12 and changes

Table 2 Mean raw scores on neuropsychological testing: baseline, at week 12 and changes

Cognitive domain	Test	*N*	Baseline	At week 12	Change from baseline to week 12		
			Mean (SD)	Mean (SD)	Mean (SD)	*t*	*P*
Processing speed	TMT A	17	51.35 (15.31)	46.35 (13.89)	−5.00 (10.41)	1.98	0.065
	Stroop image	18	40.28 (8.87)	37.28 (7.63)	−3.00 (3.58)	3.55	**0.002****
Attention	Hit rate	14	67.32 (22.20)	67.80 (19.46)	0.47 (15.41)	−0.12	0.910
	FA	14	12.24 (13.02)	11.43 (12.96)	−0.81 (2.78)	1.10	0.293
	d'	14	1.95 (1.21)	1.99 (1.13)	0.04 (0.59)	−0.24	0.813
Short term memory	Auditory span	17	5.88 (0.92)	5.88 (0.1.16)	0.00 (1.00)	0.00	1.000
	Visuo-spatial span	17	5.41 (1.12)	5.59 (1.22)	0.18 (1.42)	−0.51	0.616
Long term memory	15 Words	17	11.24 (3.01)	10.35 (3.79)	−0.88 (3.46)	1.05	0.273
	Rey figure	17	19.88 (7.93)	22.06 (6.37)	2.18 (7.91)	−1.13	0.301
Executive functions	Fluency	17	32.53 (5.62)	33.12 (8.78)	0.59 (7.55)	−0.32	0.752
	Stroop inhibition	18	59.17 (22.81)	51.94 (10.07)	−7.22 (19.18)	1.60	0.129
	TMT B	17	81.41 (27.53)	68.35 (26.86)	−13.06 (20.06)	2.68	**0.016***

TMT Part A, Trail Making Test Part A, time in seconds; Stroop image, Stroop task, denomination of image part, time in seconds; Hit rate, CPT, mean success rate, percentage; FA, CPT, false alarm rate, percentage; d', CPT, sensitivity; auditory span, number of recalled numbers; visuospatial span, number of sequences correctly recalled; 15 words, Rey Auditory Verbal Test, number of words correctly recalled; Rey figure, complex figure of Rey, points; fluency; number of words expressed; Stroop inhibition, Stroop task, interference part, time in seconds; TMT B, Trail Making Test Part B, time in seconds. * $P < 0.05$; ** $P < 0.01$

of the symptoms (changes in CGI entered as covariate), this effect was only a trend regarding the denomination part of the Stroop task, $F(1, 16) = 3.54$; $P = 0.078$; $\eta_p^2 = 0.18$, and disappeared in the Part A of the Trail Making Test $F(1, 15) = 0.781$; $P = 0.391$; $\eta_p^2 = 0.00$. The Part B of the Trail Making Test showed significant differences between both administration ($P = 0.016$). This differences remained significant even after controlling for the amelioration of the severity of the symptoms (changes in CGI entered as covariate), $F(1, 15) = 4.82$; $P = 0.044$; $\eta_p^2 = 0.24$. Small changes that did not reach significance were found for the remaining tests. These differences were not influenced by substance abuse as well as by comedication as there were no significant differences in function of these variables, both at baseline and after 12 weeks.

Relation Between Cognition and Clinical Status

Then, we conducted correlation analyses with Pearson's correlation in order to observe if the improvement in clinical status were related to improvement in the cognitive abilities. The analyses revealed no significant correlations between the improvement in symptomatology and cognition.

Impact of the Doses on the Changes in Cognition and Clinical Status

The quetiapine doses' groups did not differ in their number of male/female ($\chi^2_{(1)} = 0.2$, $P = 0.658$), substance abuse ($\chi^2_{(1)} = 1.7$, $P = 0.193$) or concomitant medication ($\chi^2_{(1)} = 2.2$, $P = 0.138$). Thus, 2 (doses: higher or lower than 300 mg/day) × 2 (time: baseline vs. after 12 weeks) ANOVAs tested the effects of doses on the improvement of cognition and clinical status. The interaction effect was of particular interest in order to observe different influence of quetiapine doses on cognition and clinical status. The results revealed a significant interaction effect on the number of words recalled on the audio span task, $F(1, 15) = 4.64$; $P = 0.048$, $\eta^2_p = 0.24$; on the time to realize the interference part of the Stroop task, $F(1, 16) = 5.14$; $P = 0.038$, $\eta^2_p = 0.24$; and on the positive scale of the PANSS, $F(1, 17) = 6.53$; $P = 0.020$; $\eta^2_p = 0.28$. Figure 1 illustrated these interactions. One could observe that lower doses showed more efficient improvement on verbal memory, inhibition and positive symptoms. However, *t*-test comparing the groups at baseline or after 12 weeks did not reveal significant differences.

Completers Versus Noncompleters

At baseline, no significant difference between the patients who did and did not complete the study was found regarding the PANSS and CGI. Regarding the cognitive measure, the completers differed from the non-completers in their performances in the fluency task ($P = 0.005$), non-completers giving less responses than completers.

Discussion

In this study, the clinical impact of quetiapine on positive and negative symptoms, as well as on general psychopathology (Table 1) confirms previous findings about positive effects of atypical antipsychotic medication [18, 19, 41] and of quetiapine both in adults [14, 20–22] and in adolescents [9, 17]. With regard to the effects of quetiapine on cognition, after 12 weeks of treatment, a significant improvement was observed in the executive function, more specifically in shifting abilities (Table 2), which remained significant after controlling for symptoms amelioration. This ability to shift between two or more tasks, operations or mental sets, refers to executive functions. Executive functions are important processes when using routines is not possible and to serve goal-directed behavior [42]. Thus, improvement in such abilities allows for better planning and problem-solving, for example. In contrast, processing speed seemed to improve, but this improvement was more related to the amelioration of the symptoms as the effect disappeared after controlling for this amelioration. Short-term memory, long-term memory and attention remained stable. These results were similar to those found in adults with psychosis, for whom significant executive functions improvements related to quetiapine's treatment have been found in shifting [14, 43] and inhibition abilities [44]. However, the present results contrast with those

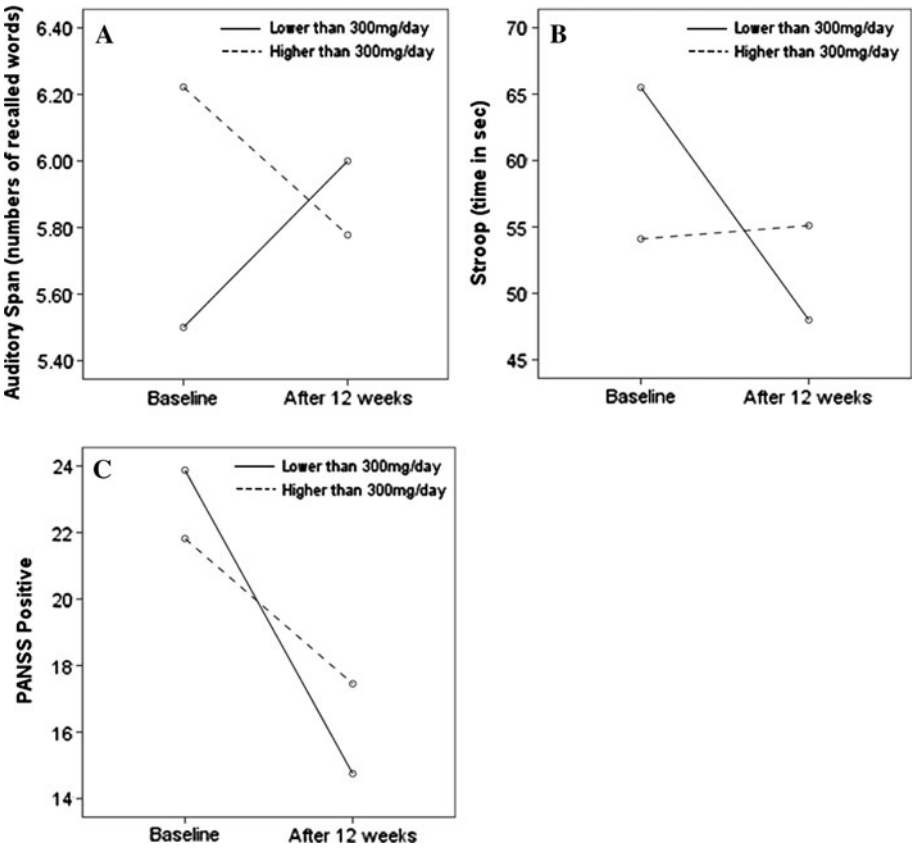

Fig. 1 Quetiapine doses by time interactions. *Note* Interaction effect between quetiapine doses and time for the auditory span (**a**), for the interference part of the Stroop task (**b**), and for the positive symptoms scale of the PANSS (**c**)

obtained by Robles et al. [9] comparing the effect of quetiapine and olanzapine on cognitive abilities of adolescents over 6 months who reported no amelioration of these abilities.

Treatment doses used in this study (350 ± 213 mg/day quetiapine) were inferior to those usually administered in the adult population. However, a high variability in the administered quetiapine doses was also reported in previous trials with adolescent patients: 532.8 ± 459.6 mg/day (reported in [9, 17]). Regarding the treatment's doses, inconsistent results were found in adult populations. Thus, Arvanitis and Miller [45] demonstrated that doses from 150 mg/day were efficient in adult populations to reduce positive symptoms but that doses of 300 mg/day at least are required to decrease negative symptoms. In contrast, Small et al. [46] demonstrated in adult populations that lower doses than 250 mg/day might not be less efficient in order to improve positive symptoms. In adolescent populations the effective doses in order to improve clinical status seemed to vary between studies. Shaw et al. [21] administered 467 mg/day (ranging from 300 to 800 mg) and Swadi et al. [22] reported a mean administered dose of 607 mg/day and reported that 4 participants out of 11 had to receive higher doses than 1,000 mg to be effective. However, in the present study, although the whole group showed improvement in clinical status, the adolescents who

tolerated only lower doses seemed to show more improvement in positive symptoms than the patients receiving higher doses.

With regard to the cognitive abilities, the same interaction was found (Fig. 1) in inhibition and verbal short-term memory. Thus, participants receiving lower doses of quetiapine demonstrated more improvement in verbal short-term memory and inhibition of automatic response compared to adolescents with higher doses of quetiapine. Both cognitive abilities are important in everyday life. Thus, short-term retention of information helped to restrain information in many situations of life and resisting to automatic behavior in favor of a non dominant one allowed adopting more appropriate behavior. Contrasting results were found in adults with schizophrenia. Velligan et al. [11] suggested that 600 mg/day doses of quetiapine allow a higher improvement in executive function and verbal memory than lower doses (300 mg/day). Nevertheless, to our knowledge, no study explored the efficiency of different doses in adolescent populations. Thus, quetiapine could have different impact according to the chronicity of the illness and the age of the patient. Indeed, some studies demonstrated that compared to those with chronic illness, treatment, even with lower doses (often 50% lower than doses for chronic patients), of individuals in first-phases of psychosis tended to be more efficient in terms of symptoms reduction [47–49]. These effects could be explained by the changed sensitivity of D_2 receptors due to long-term treatment [50]. Considering all above studies, further trials are warranted to determine the more effective doses of quetiapine in order to treat psychotic symptoms and improve cognitive abilities in adolescent populations.

The action of quetiapine in the brain could help us to understand this result. Quetiapine is associated with the occupancy of D_2 (dopamine) and $5HT_{2a}$ (serotonin) receptors which mediates antipsychotic effect (for a recent review see [51]). In adult populations, data suggested that lower doses than 450 mg/day did not allow an adequate occupancy of the D_2 receptor [46, 52–54] and so would not be effective. However, no study explored the effect of quetiapine on brain of adolescents where the necessary occupancy of D_2 and $5HT_{2a}$ receptors could be sufficient at lower doses of quetiapine or that the effective occupancy of receptor could be reached with lower doses. Further studies are needed to determine the efficient doses of quetiapine to have a sufficient occupancy of D_2 receptor. These considerations, however, neglect the fact that, as presented in the Introduction, quetiapine also exerts by its metabolism to norquetiapine, agonistic serotonergic (as a partial 5-HT1a) and noradrenergic (as a noradrenaline reuptake inhibitor) effects [24, 51]. These neurotransmitters have an important impact on psychomotor and vigilance functions, respectively [52]. Due to the non-availability of norquetiapine for analytical purposes, it could not be analyzed in this study, but a previous investigation shows that in schizophrenic patients treated with quetiapine, norquetiapine is present in measurable concentrations both in plasma and CSF [55]. In addition, the treatment resulted in a 35 and 33% increase in CSF 5-HIAA and MHPG, metabolites of serotonin and noradrenaline, respectively. Moreover, significant correlations were calculated between norquetiapine concentrations in CSF and the changes of 5-HIAA ($P < 0.01$) and MHPG ($P < 0.03$) CSF levels.

Limitations of the present study emanate from the study design. Despite the fact that the study was planned and executed by independent practitioners and data analysis was verified by an independent statistician, this was an open-label study, with no control group. There is no indication of spontaneous recovery. Moreover, associations between cognitive and clinical improvements are likely to appear at a general level, but are not necessarily found at the individual level [56]. In addition, as the group was divided a posteriori in function of the effectiveness and side effect of quetiapine treatment, further studies are

needed, in order to explore in more details the effect of low doses of quetiapine on cognition and clinical status. Finally, practice effect may have interfered in the evaluation of the cognitive improvement. However, a study conducted on schizophrenic outpatient showed a very low rate of practice effect over 10 weeks on tests used in the present study such the TMT, HVLT or the forward and backward digit recall [57]. Consistently, a previous study reported a lack of test–retest effect in first-episode schizophrenic patients [14]. A further limitation of the study is the prior treatment by other antipsychotics for some patients ($N = 8$). However, those patients were enrolled because of a lack of efficacy of the treatment and therefore during the study the patients were treated only with quetiapine. Furthermore, our analyses revealed no differences at baseline or at the end of the study when we compared the patients who take previously an antipsychotic or those who did not take previously an antipsychotic medication.

In conclusion, as cognitive functions play a major role in predicting psycho-social functioning [7, 8] and as adolescence is a critical period of development in many aspects of life, it is important to develop effective therapeutic programs which target cognitive impairments. Given the greater cerebral plasticity in this age-group, approaches which combine antipsychotic medication and cognitive remediation may enhance treatment effects and may be worth investigating. However, further studies are needed to ensure that the core feature, i.e. cognitive dysfunctions, in adolescence psychosis can be targeted by medication and/or cognitive remediation, and that substantial improvement is followed by better functional outcome. Finally, by its unique pharmacological profile, the effects of quetiapine and especially of norquetiapine should be further examined, also in animal models of cognitive functions.

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Conflict of interest PB and UP have received honoraries or sponsorships from almost all pharmaceutical companies in Switzerland selling psychotropic drugs. In particular, they received honoraries from the manufacturer of quetiapine (AstraZeneca). Others authors reported no conflicts of interest.

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