Letters to the Editor

Methodological Issues in a Comparative Study of Ziprasidone and Risperidone

Sir: Regarding a trial recently reported in the *Journal*[1] comparing risperidone and ziprasidone in the short-term treatment of schizophrenia, we concur with the authors that "more head-to-head comparisons of antipsychotics are needed to discern the relative efficacy and safety profiles of these compounds."[(p1624)] This trial furthers progress toward good comparative research in part by illustrating some methodological limitations applicable to future research. The article contains some broad conclusions that do not appear to be supported by the reported data. Important limitations of the trial include the analytic methods (e.g., non–intent-to-treat [non-ITT] subpopulations used for primary analysis) and inappropriate dosing regimens. Such factors affect both the efficacy and safety conclusions that can be drawn from this trial.

An often-recognized source of methodological weakness in comparative studies is inappropriate dosing that accentuates treatment differences. This study is seriously flawed by the dosing regimens used for both drugs. As the authors acknowledge, the ziprasidone dose was subtherapeutic in the first 2 weeks of the 8-week study, while the risperidone dose was high throughout the study. The authors note that doses of ziprasidone at or above 120 mg/day are associated with lower rates of inadequate clinical response than lower doses, and that this dose was not achieved during the first 2 weeks of the trial. The low ziprasidone dose used during the first 2 weeks may have contributed to the poor efficacy performance of ziprasidone compared with risperidone; for patients taking ziprasidone, a higher rate of serious adverse events was reported (mostly lack of efficacy: 14.1% [21/149] vs. 1.4% [2/147]), were higher overall treatment discontinuation (36.9% vs. 29.3%) and discontinuation due to insufficient clinical response (14.8% vs. 8.2%).

The authors also correctly note that the risperidone dose range (6–10 mg/day) was "higher than that currently recommended" and "clinical response to risperidone plateaus at approximately 6 mg/day," but suggest that the comparison may be relevant because dosing "was consistent with clinical practice at the time the study was designed and conducted"[1(p1632)] (August 1995 to January 1997). According to the Risperdal prescribing information of 1993 and subsequent editions, "Doses above 6 mg/day were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended."[2] Irrespective of historical considerations, it is clear that these doses do not reflect current practice and would not be considered optimal for either drug.

Several features of the study analysis also deserve comment. First, the study was designed to show "equivalence" in efficacy (total Positive and Negative Syndrome Scale [PANSS] score) between risperidone and ziprasidone. However, "equivalence" was defined such that ziprasidone could be up to 40% less effective, a margin that might be considered clinically significant. Second, although "evaluable" patient populations are an accepted approach to analysis, this practice is usually used to exclude patients for whom either baseline or at least 1 follow-up evaluation is not available. In this report, however, the "evaluable" population excluded any patient who did not complete the first 2 weeks of the 8-week study, thus excluding 40 patients from the efficacy analysis (N = 26 for ziprasidone, N = 14 for risperidone), which is an important consideration because it represents exclusion of patients from primary analysis in a nonrandom (and unequal) fashion that would be expected to introduce bias relative to an ITT analysis. The authors state that the "equivalence" observed for the "evaluable" population was also observed for "all" patients for most endpoints; however, ITT data were not reported for the broad range of endpoints studied. Given the wide definition of "equivalence," clinically important differences or patterns in primary or secondary measures may be obscured. Regarding efficacy domains in particular, PANSS total and negative subscale scores (and PANSS-derived Brief Psychiatric Rating Scale total and core items) were reported, but PANSS positive symptom and general psychopathology subscale scores were not reported.

The problematic "evaluable" cohort analysis was not performed for safety evaluations, for which an ITT cohort was inexplicably selected instead. Given the low dose of ziprasidone and the high dose of risperidone, it would be expected that artificial bias toward poor tolerability with risperidone relative to ziprasidone would be introduced. The combined impact of the dosing regimens for each agent, along with the populations used ("evaluable" patients for efficacy and "all" patients for safety) resulted in an efficacy analysis that "corrected" for the low dose of ziprasidone and a safety analysis that did not correct for either the low dose of ziprasidone or the high dose of risperidone.

Specific measures of movement disorders were included in this study using standard and validated scales: the Simpson-Angus Rating Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale. The results with these scales are remarkably similar between the 2 treatment groups, suggesting comparable measured extrapyramidal side effect burden between the 2 drugs, a finding of particular interest considering the high doses of risperidone and the low dose of ziprasidone in the safety population. However, it is only findings from a "Movement Disorder Burden" (MDB) scale (validity and reliability not described or cited) that are reported in the abstract. Weight gain conclusions may also be subject to dosing bias, although statistics for the between-group differences are not reported and, as the authors note, only a "small increase from baseline" in mean body weight (1 kg) was reported for risperidone-treated patients.

On the basis of factors such as these, we find that the conclusion ("Both agents equally improved psychotic symptoms, and both were generally well tolerated, with ziprasidone demonstrating a lower MDB score and less effect on prolactin and weight than risperidone"[1[p1624]]) may be misleading or inaccurate. Given the serious limitations of the design and analysis, the applicability of this trial's results, both efficacy and safety/tolerability, to patient care are unclear.

It is important that we continue to critically evaluate whether newer chemical entities are capable of producing superior, sustained, or even comparable efficacy relative to existing "gold standard" options. Of special note, we applaud the authors' reporting of this clinical trial, conforming to the spirit of research disclosure espoused by the Pharmaceutical Research and Manufacturers of America (PhRMA; www.phrma.org). Even when subsequent information may eclipse the value of old or limited trial designs, it remains incumbent on us to report results, point out those limitations, and make those findings available so the medical community has access to potentially relevant information.

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Dr. Addington and Colleagues Reply

Sir: We appreciate the interest in our research shown by Dr. Gharabawi and the medical affairs team at Janssen Pharmaceutica.

Dr. Gharabawi and colleagues have raised 2 main points: risperidone dose and selection of the population for evaluation of efficacy and safety. Mean total daily doses were 7.4 mg and 114.2 mg for risperidone and ziprasidone, respectively.[1] The mean risperidone dose was therefore well within the recommended dose range for risperidone.[2] For example, the risperidone package insert noted then (and currently) that a 4-week placebo-controlled risperidone study in acute schizophrenia comparing fixed dosages of 4 and 8 mg/day found that, for multiple measures of psychopathology, "results were generally stronger for the 8 mg than for the 4 mg dose group."[2]

For many clinical trials, a common criticism is that the dose of the standard comparator was too low, thus potentially biasing in favor of the newer drug under study. We note that this is not the case here—the concern is that the dose of risperidone was too high. However, the risperidone dose range used in our study is unlikely to have resulted in any bias against its efficacy based on available risperidone dose-response data. Thus, the principal study finding that ziprasidone and risperidone were equivalently efficacious in the treatment of acute schizophrenia could not have been compromised by the dose range used for risperidone. Clinical experience has been a key factor in defining optimal dosing for all second-generation antipsychotic agents. In our study, the ziprasidone dosage was fixed at 80 mg/day for the first week and then adjusted at weekly intervals in increments of 40 mg/day, while the risperidone dosage was titrated to 6 mg/day within the first week. It is reasonable to speculate that a more rapid ziprasidone dose titration may have resulted in further efficacy, given current clinical standards for ziprasidone dosing. For example, in a similar but more recent comparative study versus olanzapine, the ziprasidone daily dose was increased to 160 mg by day 3.[3]

The letter also disputed the analytic methods used in our report, particularly the selection of an evaluable population for the primary efficacy analysis. The primary study objective was to evaluate the equivalence of ziprasidone and risperidone. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH [E9]) guidelines note that "the results of using the full analysis set may be biased toward demonstrating equivalence."[4] The ICH guidelines also state that "in an equivalence or noninferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully."[5] Therefore, use of the evaluable (or per-protocol) population was entirely consistent with ICH (E9) guidelines. The population of evaluable subjects was defined prospectively in the study protocol. The criteria for this population included receipt of at least 14 days of double-blind treatment and occurrence of no major protocol violations or deviations. These protocol-defined restrictions on dose escalation (limiting ziprasidone dosage to 80 mg/day, vs. risperidone 6 mg/day at day 7) may have led to a higher discontinuation rate among ziprasidone subjects, thereby influencing the efficacy results in the full analysis set. A minimum 14-day period of drug exposure (while defined a priori) helped ensure a valid comparison between treatments.

Equivalence of the 2 treatment groups was determined by the ziprasidone/risperidone ratio of the mean change from baseline to last visit, with the lower limit of the 2-sided 95% confidence interval for this ratio prospectively defined as 0.6. In fact, as noted in Table 4 of the published study,[1] ziprasidone exceeded this limit for both primary and secondary measures of psychopathology (observed lower limits were 0.78 and 0.70 for the primary Positive and Negative Syndrome Scale [PANSS] total and Clinical Global Impressions-Severity of Illness scale [CGI-S], respectively; the observed lower limits were 0.80 and 0.81 for the secondary PANSS negative subscale and Global Assessment of Functioning, respectively). Furthermore, as shown in Figures 1 and 2 of the publication,[1] comparable mean changes in PANSS total scores and CGI-S scores were observed. These findings provide robust evidence for the comparable efficacy of ziprasidone and risperidone.

Use of the all-subjects (intent-to-treat) population for the safety evaluation and reporting was also consistent with ICH (E9) guidelines, which recommend that "subjects who received at least one dose of the investigational drug" be included in this assessment.[6(p32)] This is standard good reporting practice and therefore was not "inexplicably selected."

The letter also raised an objection to our use of the Movement Disorder Burden index. This index was protocol defined and constructed a priori in an attempt to integrate a larger number of relevant variables concerning movement disorder adverse effects than are incorporated in any of the standard rating instruments. This innovative metric accounts for movement disorder severity, adverse event duration, need for concomitant medication treatment, and total number of treatment days. It is therefore not limited to single-scale, cross-sectional assessment of movement abnormality at baseline and endpoint, and it sensitively reflects the overall burden imposed by the development of movement disorders. The ability of this index to differentiate between treatments was established in this study by the demonstration of a significantly lower movement disorder burden for ziprasidone compared with risperidone. Risperidone was also associated with a consistently greater adverse effect on prolactin levels in both men and women; it is not clear to us why the authors view this statement as potentially misleading.

With regard to the final point, that newer agents should be critically assessed in comparison to "gold standard" options, we found that in this double-blind study of patients with acute schizophrenia, ziprasidone demonstrated equivalent efficacy to risperidone and was associated with little or no increase in prolactin levels, weight, and movement disorder burden, in contrast to risperidone. These conclusions were well supported by the

rigorous design, analysis, and reporting of this randomized, controlled study.

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Methodological Concerns Regarding the Relation Between Mefloquine and Serious Psychiatric Events in Females

Sir: van Riemsdijk et al.[1] report the results of a case-control study of serious psychiatric events related to mefloquine use among Dutch travelers. A highlighted result is a (startling) odds ratio (OR) of 47.1 (with very wide 95% CI of 3.8 to 578.6) for such events in females taking mefloquine.

While the basic case-control methodology of this study appears sound, we have concerns that would erode confidence in this study: (1) The overall response rate from cases and controls is felt, by the authors, to be high enough ("almost 70%") to avoid selection bias. However, overall, in the important analysis reported in Table 2, only 58% of cases (107/185) and 44% of controls (445/1017) were included. (2) It would appear that cases and controls, while matched on "continent of travel," might not have been at equal risk of being exposed to antimalarials (including mefloquine); per Table 1, 32% of cases but only 22% of controls used antimalarial drugs. (3) It would be biologically unexpected that females would have 19 times the OR of males for serious psychiatric events using mefloquine (47.1 vs. 2.5), none of which would, on the surface anyway, appear to be heavily related to specific female physiology. (4) The authors discount the role of "recall bias." However, the issue of neuropsychiatric adverse events related to mefloquine had likely been given substantial attention by the media during the timeframe of this study (1997–2000), and it may well be that cases would differentially remember use of mefloquine compared with controls. (5) The authors use the missing indicator method to account for missing values; however, there have been cautions[2,3] against using this method.

To us, the important, data-based finding in this study is that travelers with a known contraindication to mefloquine were prescribed mefloquine; i.e., per Table 3, 16% of cases with a known history of psychiatric disease were prescribed mefloquine.

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Dr. Stricker Replies

Sir: My colleagues and I highly appreciate the interest in our article[1] by Dr. Tepper and Ms. Strauss. My response will follow the sequence of their 5 points.

First, the questionnaire response rate in our study was 67%, 63% for cases and 67% for matched controls (intended case: control ratio = 1:6). This difference in response rate was not statistically significant. This similarity might be expected given that cases as well as controls had serious physical reasons to contact their homeland and most of them were willing to participate. Because we could not use controls for nonresponding cases in the matched analysis and vice versa, the analysis was indeed performed in a smaller group, but we do not expect that this technical reason might have introduced a bias. Second, we matched on continent of travel. Because mefloquine is such a strong risk factor for neuropsychiatric disease, it is not very surprising that there were more users of antimalarials in cases than in controls. Third, a difference between females and males is not biologically unexpected. One of my coauthors demonstrated that females had significantly higher blood levels of mefloquine

than males.[2] Moreover, the expression of P-glycoprotein might differ between males and females,[3] which might explain higher concentrations of mefloquine in the female brain. My colleagues and I also found a higher risk of neuropsychiatric effects in females in a double-blind clinical trial setting comparing atovaquone plus chloroguanide versus mefloquine, which excludes potential bias and confounding.[4]

Fourth, my colleagues and I think that recall bias is unlikely as no such effect was seen in males. All study participants suffered from serious conditions, and one might expect enhanced recall for both cases and controls and for both males and females. Fifth, we are aware that there are cautions against the missing indicator method when used for adjustment. We used missing indicators, however, only to judge whether the missing status acted as a confounder. As this was not the case, adjustment was not necessary.

Finally, my colleagues and I would like to emphasize that there is abundant evidence that mefloquine causes neuropsychiatric adverse reactions and that these reactions are more common in females than in males.[2,4–6]

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Propofol for Severe, Refractory Mania: A Case Report

Sir: Treatment options for severe refractory mania are limited.[1] We present our experience with a patient whose severe, refractory mania was unresponsive to electroconvulsive therapy (ECT), but whose clinical course eventually improved following the initiation of propofol. The literature has sparse documentation of the use of propofol in this setting,[2] but this sedative-hypnotic agent was used safely and effectively in our experience.

Case report. Ms. A, a 49-year-old woman with a history of bipolar disorder, type I (DSM-IV), was admitted in 2000 with elevated mood, grandiosity, decreased sleep, loud and pressured speech, racing thoughts with flight of ideas, distractibility, and psychomotor agitation. Symptoms were present for 3 weeks prior to admission. Laboratory values on admission were notable for a negative urine drug screen, basic metabolic panel and complete blood cell count within normal limits, and serum valproic acid level of 72.5 μg/mL.

The patient was initially treated with divalproex sodium (1000 mg twice a day) and lorazepam (5 mg/day), with symptom improvement after 8 days. She elected to participate in a study protocol, and after informed consent was obtained, divalproex and lorazepam were tapered. Manic symptoms reemerged. The study protocol was terminated after 1 week due to the severity of her symptoms.

Divalproex sodium, risperidone, and lorazepam were then started, with no change in the patient's symptoms. As she had been maintained on haloperidol decanoate with risperidone in the past, haloperidol was added owing to her worsening paranoia and severe agitation. Her symptoms continued to worsen, and her sleep and appetite dropped off precipitously. She continued to be agitated, labile, disorganized, and aggressive. Droperidol was used selectively for extreme agitation (10 mg given intramuscularly), and chloral hydrate (in doses of 1000 mg) was used for sleep.

On hospital day 37, she was found to be diaphoretic and had an elevated pulse (126 beats per minute) and blood pressure (152/96 mm Hg), as well as muscle rigidity. She had a mildly elevated temperature of 99.8°F, and her creatine phosphokinase (CPK) level was 11,651 U/L. She was awake and responsive but not fully oriented, and after discussion and consultation with the medicine service it was felt that her condition may represent early neuroleptic malignant syndrome. All neuroleptics were discontinued, and the patient was transferred to the medicine service for treatment of suspected neuroleptic malignant syndrome.

The patient was transferred back to the psychiatric ward after 6 days at the medicine service. Her CPK level had been as high as 28,183 U/L. At the time of transfer, her CPK level was 677 U/L, and this ultimately returned to within normal limits. She was continued on divalproex sodium (up to 3000 mg/day), but she continued to be labile, irritable, threatening, and intrusive and had flight of ideas as well as limited intake of food and markedly reduced sleep (often not sleeping at all during a 24-hour period). She continued to require multiple interventions due to her agitated and often aggressive and threatening behavior.

An ECT consultation was obtained, and divalproex sodium was discontinued in preparation for her first treatment. She received 6 treatments of ECT, and despite some initial improvement she remained labile with disorganized and pressured speech as well as psychomotor agitation and flight of ideas with occasional "word salad." Chlorpromazine (200–400 mg per dose), chloral hydrate (in 1000-mg doses), and amobarbital (in 250-mg doses) were used in between her ECT treatments in an attempt to control her continued agitation, but these agents provided her no relief and her agitation became so severe that ECT could not be performed on one occasion. She developed worsening paranoia and was increasingly guarded, irritable, agitated, and aggressive, and she continued to sleep, eat, and drink very little. Due to her severe and refractory symptoms and lack of response to ECT, the treatment team discussed the possibility of the use of propofol with the neurology, anesthesiology, pharmacology, and pulmonary medicine services. It was decided that treatment with propofol would be attempted. Consent was ob-

tained from the patient's family, and she was transferred to the medical intensive care unit (MICU) on hospital day 55.

A protocol for the use of propofol in this case was developed in consultation with a pharmacologist, an anesthesiologist, a neurologist, and a pulmonary intensivist. The patient was electively intubated by the anesthesiologist and started on an intravenous propofol drip. The rate was titrated in order to achieve full sedation and was increased to 65 µg/kg per minute within 1 hour and was then further increased to 75 µg/kg per minute after another 7 hours. The rate was maintained between 75 and 85 µg/kg per minute over the next 51 hours, at which point propofol was tapered and discontinued. After the drip was discontinued the patient was extubated and divalproex sodium was started at 750 mg by mouth twice a day. Creatine phosphokinase levels were within normal limits throughout her stay in the MICU, and she was transferred back to the psychiatric ward 5 days after being admitted to the MICU.

When she returned to the psychiatric unit, she was initially sedated and not fully oriented and had intermittent mild agitation, paranoia, and tangential thought process but was cooperative and had less pressured speech. She was much less irritable, and her sleep and appetite steadily improved. She did not require seclusion, and despite some episodes of irritability her symptoms continued to improve. Divalproex sodium was titrated to 1000 mg twice a day, and chlorpromazine was added at 200 mg twice a day and 100 mg as needed for breakthrough agitation. Olanzapine was titrated to 10 mg each night in anticipation of discontinuing chlorpromazine in the outpatient setting. She had no adverse reactions to these medications, and she was discharged on hospital day 72, 13 days after the completion of 60 hours of general anesthesia with intravenous propofol.

This case highlights a viable option that could be considered when the usual medications and interventions used to treat refractory mania are unsuccessful. Severe mania, refractory to high doses of antimanic and antipsychotic drugs, can constitute a psychiatric emergency. While few treatment options are available for this situation, we found that the use of propofol was successful in 1 patient. It should be noted that our patient was electively intubated and propofol was administered at doses consistent with those used for general anesthesia. The previous case report by Fox and Bostwick[2] described using a lower infusion rate of 10 to 50 µg/kg/min on an intermittent basis. The authors noted that the patient was not ventilated, although they recommended that this procedure be done in a setting in which artificial ventilation can be applied if needed. Their report focused on the use of propofol for the purpose of treating the patient's agitation and allowing for the completion of a course of ECT. Our case report differs considerably from theirs in that we used propofol as a treatment in and of itself and thus utilized doses used for general anesthesia. This necessitated collaborating with physicians and staff in several other disciplines in order to develop a protocol and administer the medication safely and appropriately.

Propofol is an intravenous anesthetic with central nervous system depression resulting from its unique structural resemblance to γ-aminobutyric acid (GABA). It is thought that propofol acts to facilitate GABA-A receptor activity and depresses glutamate synaptic transmission. It acts quickly and is rapidly cleared with little bioaccumulation. There have been reports of the use of propofol for the treatment of alcohol withdrawal[3–6] and agitation,[7,8] and it is thought that its effects on the GABA and glutamatergic systems result in its efficacy in these clinical situations. However, only 1 other case report[2] has discussed the use of this medication in refractory mania, although in that case it was used at lower doses and for the purpose of sta-

bilizing the patient so that ECT could be administered. In our case, the patient's mania was refractory to ECT and propofol was used as a pharmacologic treatment. Given the putative role of GABA, glutamate, and the GABA receptor in bipolar illness, one would have to wonder if there was an effect more than just sedation that was obtained from propofol in the treatment of this severe and refractory manic episode.

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Galantamine-Induced QTc Prolongation

Sir: Galantamine is an acetylcholinesterase inhibitor that is approved for the treatment of mild to moderate Alzheimer's dementia. It may also have beneficial effects in the treatment of schizophrenia.[1,2] The following is a case report of a patient with schizophrenia who developed corrected QT interval (QTc) prolongation while receiving galantamine.

Case report. Mr. A, a white man aged 47 years at the time of this report, had a history of DSM-IV schizophrenia as well as diabetes, hypertension, and hyperlipidemia. At the time of presentation (2004), his psychotropic medications were aripiprazole, 30 mg/day; quetiapine, 1000 mg/day; lithium, 1200 mg/day; benztropine, 1 mg/day; and trazodone, 200 mg as needed for sleep. Other (nonpsychotropic) medications at the time of presentation included aspirin, docusate, enalapril, insulin, lactulose, metoprolol, ranitidine, simvastatin, and vitamin E. After providing written informed consent, Mr. A was started on treatment with galantamine at a dose of 8 mg/day (4 mg b.i.d.). Immediately prior to initiation of galantamine, his QTc was 417 msec and his heart rate was 71 bpm. His QTc interval had ranged from 420 to 443 msec on his annual electrocardiogram (ECG) in the 5 years prior to starting galantamine, and an additional ECG 3 months prior to the initiation of galantamine revealed a QTc of 415 msec. No changes were made to his medication regimen during his treatment with galantamine. His

serum lithium level 1 month after galantamine initiation was 0.44 mEq/L.

After titration of galantamine to 12 mg b.i.d. over 2 months, another ECG was performed and revealed a QTc of 518 msec (heart rate = 70 bpm). Mr. A's only complaint at the time was transient leg weakness. Serum potassium, magnesium, and calcium levels were within normal limits. Galantamine was discontinued immediately, and his QTc shortened to 459 msec and 414 msec, 1 and 2 weeks, respectively, after stopping the drug.

To our knowledge, there have been no reports of QT prolongation associated with galantamine. There has been 1 report of QT prolongation with the acetylcholinesterase inhibitor rivastigmine in an elderly man with dementia.[3] Our patient had several risk factors that may have contributed to the development of a prolonged QT interval. He had a complex medication regimen including psychotropic drugs that may have an effect on QT interval (i.e., quetiapine and lithium).[4] However, his medications had been consistent for 4 months prior to his taking galantamine, and the 2 ECGs performed while he was on this medication regimen, but prior to starting galantamine, demonstrated a QTc of 415 and 417 msec. Other risk factors included his diabetes mellitus and likely heart disease based on the presence of syndrome X. While these risk factors may have played a role in this patient's QTc prolongation, the temporal relationship of QTc prolongation with the initiation of galantamine treatment and subsequent decrease after its discontinuation implicates the drug's involvement.

Although this case of QTc prolongation occurred in a middle-aged man with schizophrenia, the population most likely to receive galantamine is one consisting of elderly dementia patients. Patients in this population are likely to have a number of risk factors for QTc prolongation, including complex medication regimens and comorbid medical conditions, and may warrant situational cardiac monitoring during treatment with acetylcholinesterase inhibitors.

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