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Antipsychotic Drugs in Autistic Children using LC/MS-MS: Better-Fixed Doses Necessary for the Middle East

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Abstract: This study aims to investigate the effectiveness of drug doses prescribed to autistic children in the Middle East. The uniqueness of this study relies on the fact that fewer research profiles in this study area are available in the Middle East. Specifically, this study presents recommendations based on accurate measurements in plasma compared to the prescribed doses. Plasma samples from 18 children were collected. Levels of olanzapine, risperidone, and quetiapine drugs were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS). This is a powerful accurate analytical tool in which the coefficient of determination (R^2) was greater than 0.998. The coefficient of variation and relative error was less than 15%. Steady-state concentrations for the previously mentioned drugs were less than the determined concentration in plasma. A better-effective treatment for people affected by autism spectrum disorder (ASD) is needed to reduce/eliminate the side effects as well as increase the effectiveness to achieve the best outcome. For improvement functions, better fixed doses of the medications were necessary for better performance. In addition, increasing awareness of the importance of finding a better-effective treatment for people affected by autism spectrum disorder (ASD) is essential. This will optimize the activation/inhibition of some enzymes. More effective treatment guidelines must be developed for patients with ASD.

Keywords: autism spectrum disorder, olanzapine, risperidone, quetiapine, children's health, drug dose, liquid chromatography-tandem mass spectrometry.

自闭症抗精神病药物：自闭症儿童的血浆水平、可能的后果以及在中东需要更好的固定剂量

摘要：本研究旨在调查中东地区自闭症儿童处方药物剂量的有效性。本研究的独特性依赖于这样一个事实，即中东地区在该研究领域的研究资料较少。具体来说，本研究根据血浆中的准确测量值与处方剂量相比提出建议。收集了 18 名儿童的血浆样本。使用液相色谱-串

联质谱法 (质谱/质谱) 测定奥氮平、利培酮和喹硫平药物的水平。这是一个强大的精确分析工具, 其中测定系数 (R2) 大于 0.998。变异系数和相对误差都小于 15%。前面提到的药物的稳态浓度小于血浆中的测定浓度。需要对受自闭症谱系障碍 (自闭症谱系障碍) 影响的人进行更有效的治疗, 以减少/消除副作用, 同时提高疗效, 达到最佳效果。为了改善功能, 需要更好的固定剂量的药物, 以达到更好的效果。此外, 提高对为受自闭症谱系障碍 (自闭症谱系障碍) 影响的人寻找更好的有效治疗方法的重要性的认识至关重要。这将优化一些酶的激活/抑制作用。必须为自闭症谱系障碍患者制定更有效的治疗指南。

关键词: 自闭症谱系障碍、奥氮平、利培酮、喹硫平、儿童健康、药物剂量、液相色谱-串联质谱法。

1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental syndrome that originates from undetermined causes [1]. It is a developmental disorder because symptoms usually arise within the first two years of life [2]. In the USA, the percentage of children with ASD was 0.67% in 2000 and increased to 1.85% in 2016. ASDs represent three known developmental disorders: autistic disorder (AD), Asperger's Syndrome (AS), and pervasive developmental disorder not otherwise specified (PDD-NOS) [3]. The unusual social interaction is disturbed either verbally or nonverbally, and the presence of highly restricted interests and repetitive behavior is used to define ADS [1], [4]-[5]. Recent studies have affirmed that autism has many etiologies and linked them to numerous causes and factors. Environmental, pathological and neurobiological factors play a role in autism [1]. However, until now, no one has yet revealed a well-established database about the ASD etiology [5].

Heritability factor is the most muscular suggested cause of autism [1], [6]. Multiple genes could be related to autism with different phenotypic variations [5]. Additionally, a relationship was found between ASD with some syndromes and medical conditions such as Fragile X, Joubert, and Timothy syndromes [7]. Studies showed that many environmental factors could affect the genes of autism and lead to the expression of these genes [8], [9].

Unfortunately, vaccines were suggested as causative agents for ASD, in particular measles-mumps-rubella (MMR) vaccines [10]-[11] and mercury-containing vaccines [12]-[13]. Mercury is a known neurotoxin used in vaccines as a preservative (Thimerosal), and many studies have supported the association between these vaccines and autism.

Some medications have been strongly connected to autism as a significant risk factor. Misoprostol, a prescription used to induce labor, was linked to autism in which three out of five children with autism had a

history in utero exposure to misoprostol [14]. Antidepressants (especially Selective Serotonin-Reuptake Inhibitors (SSRIs)) [15], antiepileptics, most notably (Valproic acid) [16,17], and antiasthma tics especially (β -2 Adrenergic Receptor agonists (B2ARs)) [18,19]. The seriousness of these medications lies in their ability to cross the placenta blood-brain barrier. Also, they can be found in breast milk [20].

ADS is related to an unusual social interaction, disrupted communication, restricted and repetitive behaviors, interests, and activities. ADS is usually accompanied by comorbid psychiatric or medical conditions that require medical intervention. For example, acts of aggression, hyperactivity, and self-injury can be medicated with risperidone, olanzapine, and quetiapine. Olanzapine and quetiapine could be beneficial with no FDA package insert indication to be used for children with having ASD [21]. Olanzapine is a novel antipsychotic drug known for its broad efficacy, low extrapyramidal symptoms (EPS), and minimal alteration of prolactin levels [22]. It is known to increase antidopaminergic effects, including EPS and neuroleptic malignant syndrome [22]. Risperidone is an atypical antipsychotic that is distinguished by its unique receptor-binding profile. It slightly increases antidopaminergic effects, including EPS and neuroleptic malignant syndrome, and both increase sedation [23]. Clinically, quetiapine showed a low tendency to cause EPS [24].

In this study, the authors focused on the effective therapeutic drug monitoring (TDM) of risperidone, olanzapine, and quetiapine [25] for patients affected by ASD. This aim was achieved by comparing the dose taken and its level in plasma using LC-MS/MS. The similarities/differences between drug dose and blood level were discussed. Consequently, recommendations were proposed. The main steps of the research process are summarized in Figure 1.

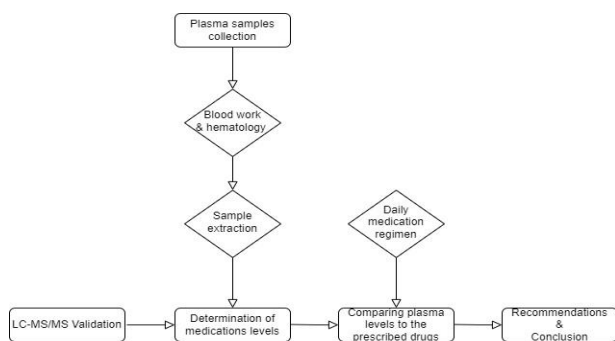


Fig. 1 Research flowchart

2. Materials and Methods

2.1. Chemicals and Reagents

Olanzapine, quetiapine, and risperidone (minimum 98% each) raw substances were obtained from Jordan Sweden Pharma Company. Chloramphenicol (Thermo Scientific™, 98%), methanol (minimum 99.9%, gradient grade), aqueous ammonia (35% solution in water, for HPLC), formic acid (minimum 99.0%, Optima™ LC/MS Grade), and water (HPLC grade) were purchased from Thermo Fisher Scientific (United States).

2.2. LC-MS/MS and Its Condition

A reliable LC-MS/MS optimized condition was developed to quantify risperidone, quetiapine, and olanzapine in human blood. LC was Agilent 1200 Series Gradient system connected to API 3200, a fully integrated triple quadrupole mass spectrometer Applied Biosystems, MDS SCIEX. LC-MS/MS was controlled by Applied Biosystems, MDS SCIEX Analyst 1.6.3 data acquisition management software system. The condition was optimized as follows. A reverse phase approach was applied using Fortis Uneversil C18 (50 × 4.6 mm, 5 μm) column at 20°C compartments. A solution of 45% (1:1 of aqueous ammonia and formic acid, 0.016% each): 55% methanol as mobile gradient phase. The flow rate was 0.80 mL.min⁻¹. The autosampler injection volume was set to 3 L at ambient temperature. The total run time was 2.5 min.

2.3. Standard Solutions

2.3.1. Stock Solutions, 1 mg/mL

1) Stock standard solution was prepared by dissolving 5 mg of each of olanzapine, quetiapine and risperidone drugs in a 5 ml volumetric flask (class A) in 2 mL methanol. The solution was vortexed for complete dissolution. The volumetric flask was topped up to mark with methanol.

2) Stock standard solution was prepped by dissolving 5 mg Chloramphenicol (internal standard) in 5 ml volumetric flask (class A) in 2 mL Methanol. The solution was vortexed for complete dissolution. The volumetric flask was topped up to mark with methanol.

2.3.2. Standard Calibration, Quality Control, and Internal Standard Solutions

1) Standard Calibration Solutions

Four low levels, 20 μL of a stock standard solution were diluted in a 10.0 mL volumetric flask (class A) with methanol aqueous solution (1:1). As a result, a standard solution of 2.0 μg/mL of each drug was prepared. In human plasma, 1.0, 2.0, 5.0, and 10.0 ng/mL were prepared as low-level calibration standard solutions.

Four high levels, 250 μL of a stock standard solution were diluted in a 10.0 mL volumetric flask (class A) with methanol aqueous solution (1:1). As a result, a standard solution of 2.0 μg/mL of each drug was prepared. In human plasma, 20.0, 40.0, 100.0 and 150.0 ng/mL were prepared as high levels of calibration standard solutions.

2) Quality Control Solutions

Four levels of quality control solutions were prepared as follows. Low 3.0 ng/mL, medium (A, 6 ng/mL), medium (B, 60 ng/mL) and high (120 ng/mL) of each drug from different batch than the standard calibration levels.

3) Internal Standard Solution

Stock standard solution (250 μL) was diluted in a 10.0 mL volumetric flask (class A) with methanol aqueous solution (1:1). As a result, a standard solution of 25.0 μg/mL of chloramphenicol was prepared.

2.3.3. Calibration and Quality Control Level Readiness

Calibration levels preparation: 10 μL of each of the four low and four high levels were added to eight 25 μL internal standards in eight labeled Eppendorf tubes. Each was vortexed for 10 seconds. A precipitation agent of 300 μL of methanol was added and vortexed for 1.0 minute and centrifuged for 5.0 minutes at 1400 rpm. An aliquot of 250 μL of supernatant was transferred to a 2 mL HPLC vial with an insert and capped ready to be injected.

Quality control levels preparation: 10 μL of each of the four levels were added to four 25 μL internal standards in four labeled Eppendorf tubes. Each was vortexed for 10 seconds. A precipitation agent of 300 μL of methanol was added and vortexed for 1.0 minute and centrifuged for 5.0 minutes at 1400 rpm. An aliquot of 250 μL of supernatant was transferred to a 2 mL HPLC vial with an insert and capped, ready to be injected.

2.3.4. Method Validation

Noteworthy, calibration curves were freshly prepared and immediately injected without carryover.

1) Linearity, Limits of Detection, and Quantification

Linearity was evaluated based on eight injected standard levels for each drug. The percentage relative error (R.E.) was less than ±15%. The slope, Y-intercept, R², LOD, and LOQ are shown in Table 1.

Table 1 Linear regression parameters for risperidone, quetiapine, and olanzapine

Drug	Slope	Y-intercept	R ²	LOD, ng/mL	LOQ, ng/mL
Risperidone	1.0153	-0.6274	0.9981	0.3	1.0
Quetiapine	1.0108	-0.4446	0.9991	0.3	1.0
Olanzapine	1.0233	-0.9559	0.9971	0.3	1.0

2) Accuracy and Precision

Four levels of quality control were used to evaluate the precision and accuracy of drugs involving the calibration curves.

Fig. 2 shows that the accuracy coefficient of variation (C.V.) and precision (R.E.) for each level was less than 15%, respectively.

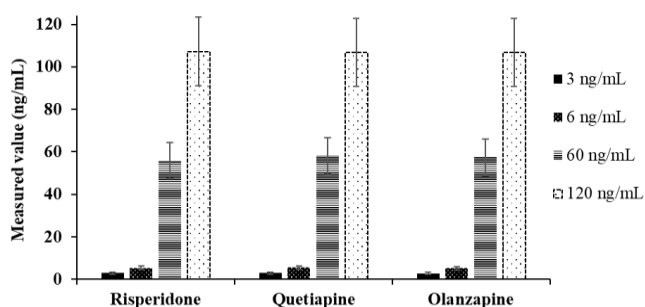


Fig. 2 Accuracy and precision for each drug including nominated and measured values

2.4. Ethical Approval and Patient Consent

The inter-regulatory board approved this study of the “Jordan Center for pharmaceutical research” on 30/1/2019. The children consented to participate with the approval of their parents in a separate consent form provided by the “Arabic Village for Special Education Center.” All procedures, interventions, and laboratory analyses were conducted according to the guidelines of the Ministry of Health in Jordan.

2.5. Demographic Data

The participants were 18 autistic cases located in the Middle East. The children were diagnosed with autism in the first two years of their life. Also, they were proved to be treated with olanzapine, quetiapine, and risperidone. The samples were collected in collaboration with the Arabic Village for Special Education Center. Children aged 4-5 years were males and had Middle East parents. All children were healthy. For blood work see supplementary materials S2. Daily medication regimens are shown in the Supplementary Materials S4.

2.6. Sample Collection

A withdrawn amount of 10.0 mL blood sample from each child was collected. It was divided into three tubes, 3.0 mL as a whole blood sample using EDTA tubes to analyze the CBC/hematology parameters. Supplementary Materials S3, 3.5 mL blood sample in an empty box was centrifuged at 3000 rpm for 5

minutes. The serum was separated for clinical chemistry analysis. The last 3.5 mL blood sample in citrate tubes was centrifuged at 3000 rpm for 5 minutes. This plasma sample was used to analyze the targeted medications using the LC/MS/MS technique at Jordan Center for Pharmaceutical Research.

2.7. Clinical Chemistry Analysis

Blood samples were used to evaluate the patient’s parameters for kidney (uric acid, urea, creatinine, sodium, potassium, and chloride), liver (Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma-glutamyl transferase (GGT), Alkaline phosphatase, total protein, albumin, globulin, bilirubin total and direct), thyroid gland (Thyroid-stimulating hormone (TSH), Triiodothyronine, free T3, Thyroxin, free T4), vitamins (B12, D), and ferritin. Also, hematology parameters are White Blood Cells (WBC), Red Blood Cells (RBC), Hemoglobin (HGB), and Platelets (PLT).

2.8. Liquid-Liquid Extraction Method

Sample preparation: 10 µL of a plasma sample were added to 25 µL of internal standard (see supplementary materials), in a labeled Eppendorf tube. It was vortexed for 10 seconds. A precipitation agent of 300 µL of methanol was added and vortexed for 1.0 minute, and centrifuged for 5.0 minutes at 1400 rpm. An aliquot of 250 µL of supernatant was transferred to a 2 mL HPLC vial with an insert and capped ready to be injected.

3. Results and Discussion

3.1. Blood Chemistry Analysis

All blood chemistry parameters were considered normal and within range, except for three children. In the fourth sample, the GGT value was low (4 U/L). In the 8th sample, TSH was high (7.5 mIU/ml). In the last 11th sample, the creatinine level was slightly higher than usual (1.4 mg/dL). Also, the results showed that patients’ mean vitamin D level was insufficient. Several researchers have studied the relationship between ASD and vitamin D deficiency and support the possible role of vitamin D deficiency in the pathogenesis of ASD [26]-[27]. However, in the literature, there were no correlations between insufficient vitamin D levels in patients and medications (olanzapine, risperidone, and quetiapine). No correlation between creatinine, GGT, TSH, and ASD has been reported in the literature.

The CBC results showed an interesting difference compared with normal ranges. The lymphocytes and monocytes in most children were significantly higher than the normal ranges. This relationship between the levels of monocytes and lymphocytes with ASD in which high and low levels of monocytes could indicate the diagnosis [28]. Also, high levels plus ASD increase

the prevalence of specific immune-related comorbidities, including infections, allergies, and asthma. The 18 children showed a significant increase in RDW values. Increasing the RDW values increases the possibility of chronic inflammation [28].

RBC, MCV, and HCT values significantly decreased for all children, except for sample 6. The low levels of these indices usually indicate iron deficiency. Samples number (2, 15, 17, and 18) showed a significant decrease in their hemoglobin (HGB) levels. This supports the suggestion of the existence of one of the medical cases of iron deficiency, anemia [29]. Children with ASD may have a deficiency in iron [30]. Children with anemia may develop new skills compared to healthy ones, which could make ASD more severe [31]-[32].

Clinically, a significant increase in MCHC values was observed in all samples with no exceptions. In this study, MCH values for 15 samples were significantly high, except for samples 6, 17, and 18. This could also be due to deficiencies in vitamins (folate in particular) [33]. Samples number 1, 2, 3, 8, 14, 15, and 16 showed a significant increase in their platelet count; high platelet counts could be a result of many diseases including blood loss, infection, an inflammatory disorder, or even cancer [33].

3.2. Determination of Olanzapine, Quetiapine, and Risperidone in Plasma

For olanzapine, the recommended dose is 10-20 mg/day [25]. The TDM concentrations at the plasma level should be 20-80 ng/mL [34]. As shown in Table 2, the prescribed dose for the child of sample number 1 was 100 mg/day, which is more than the recommended dose by ca. 5-10 folds. However, the concentration in plasma was 2.4 ng/mL. This could be due to a child not taking the medication precisely. The prescribed dose of olanzapine in sample number 5 was at the lower limit of the prescribed dose. The concentration in plasma was 12.1 ng/mL. The dose amount for this child must be increased to 20 mg/day to reach the recommended level in plasma. Samples 8 and 12 must be increased four-fold. A relationship between the prescribed dose of the drug and its bioavailability in a human body, e.g., in plasma, is not directly proportional [35]. Therefore, a drug dose can be optimized by increasing or decreasing the dose amount. This can easily be seen in sample number 8. For optimization, the dose should be increased tenfold and then tested again. This could be related to a child's high body mass index (BMI). Samples 11 and 18 doses must be adjusted.

Table 2 Olanzapine levels in plasma samples

Sample number	Daily dose (mg)	Concentration (ng/mL)
1	100	2.39
5	10	12.09
8	5	0.30

11	20	28.71
12	5	5.71
14	20	29.50
18	5	5.33

For quetiapine, the recommended dose is 150-450 mg/day and is as effective as 750 mg/day [25]. The TDM concentrations in plasma should be 100-500 ng/mL [36]. As shown in Table 3, although samples 12 and 15 were within the recommended dose range, samples 2 and 15 were less than the TDM in plasma. To solve this issue, the daily dose for these children must be increased and monitored for optimization. Samples 10, 13, and 14 must be optimized in terms of given quantities based on BMI.

Table 3 Quetiapine steady-state concentration comparison

Sample number	Daily dose (mg)	Concentration (ng/mL)
2	250	66.6
9	200	121.0
10	25	0.22
12	400	185.5
13	50	7.35
14	100	12.78
15	200	14.6

For Risperidone (Table 4), the minimum recommended dose of risperidone is 1 mg/day, the average is 2-4 mg/day, and no more than 8 mg/day [25]. The TDM concentrations in plasma should be 20-60 ng/mL. Samples were within the dose range except sample number 12 (0.5 mg/day). All samples were below the TDM concentration in plasma. Therefore, the doses must be optimized.

Table 4 Risperidone steady-state concentration comparison

Sample number	Daily dose (mg)	Concentration (ng/mL)
2	1	1.12
3	4	2.12
4	1	4.36
5	2	6.60
7	8	2.59
11	4	3.92
12	0.5	0.70
15	2	0.98
16	2	10.93
17	5	3.45

Continuation of Table 4

18	2	9.12
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Most cases were prescribed doses low compared to TDM concentration in plasma. The authors suggested creating feedback and a better communication line between a physician and a pharmacist. This can happen through software to warning limits for the prescribed drug. For dose optimization, it is recommended to run blood checkups from time to time to monitor the TDM concentration in plasma to achieve the maximum possible performance. Also, awareness campaigns should be established to help children and parents to precisely follow a prescription written by the physician.

3.3. Side Effects and Drug-Drug Interaction (DDI)

Many patients were treated with a combination of these drugs in addition to others as; see, see supplementary materials S4. Medicines may work as enzyme inhibitors or activators. Generally, olanzapine and risperidone have more side effects compared to quetiapine. The side effects can be weight gain, high blood sugar, and increased prolactin levels [37]. Therefore, the balance between benefits and risk must be assessed to maximize the use of benefits.

In samples 5, 8, 14, and 18, olanzapine was prescribed alongside valproate. Valproate is a metabolic inhibitor (it may induce some metabolic enzymes), while olanzapine is an inhibitor [38]-[39]. The presence of valproate decreases olanzapine concentration in plasma, thereby reducing its metabolism [40]. They may affect one another in the brain transformation in an increase or decrease in their efficacy or elimination [41]. Therefore, a patient case should be closely monitored to examine if this combination improved the case. The clinical significance of plasma level alterations should be measured by the therapeutic index of these drugs in which elimination is altered. Pharmacokinetic interactions between antipsychotics arise at the metabolic level, including modifications in the activity of drug-metabolizing enzymes (the cytochrome P450 (CYP) monooxygenases and uridine diphosphate-glucuronosyltransferases) associated with their biotransformation process. The multiple CYP enzymes are divided into families, subfamilies, and isoenzymes. The CYP enzymes involved in drug metabolism include CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

The Uridine diphosphate-glucuronosyltransferases (UGTs) are enzymes found in the endoplasmic reticulum, mainly in the liver; more than 33 families of the UGT superfamily were identified and classified [42]. UGTs catalyze the glucuronidation of many endobiotic and xenobiotics [43]. The products of UGTs have lower toxicity, more water-solubility and excreted

faster than parent compounds.

The drugs studies are principally metabolized by cytochrome P-450 (CYP) enzymes, but as various isoenzymes are involved, predominantly CYP1A2 and UGT1A4 for olanzapine, CYP2D6 for risperidone, and CYP3A4 for quetiapine [44].

Risperidone is metabolized in the liver, producing 9-hydroxyrisperidone as an active metabolite [45]-[46]. This metabolite (9-OH-risperidone) mostly has similar potency as the active risperidone in dopamine receptor affinity. They are responsible for the overall antipsychotic and undesirable effects. Studies showed that risperidone is metabolized mainly by the enzymes CYP2D6 and CYP3A4 [47]-[48].

Olanzapine is metabolized directly by the enzymes UGT1A4 (N-glucuronidation) and CYP1A2 (N-demethylation) and by biotransformation catalyzed by the flavin-containing monooxygenase-3 system (N-oxidation), and by CYP2D6 (2-hydroxylation) [49]-[50]. Quetiapine, a dibenzothiazepine derivative, is metabolized in the liver majorly by CYP3A4 isoenzyme and to a lesser extent by CYP2D6 [24] sulfoxidation to form N- and O-dealkylation [45]-[46]. Variations in the interaction potential of these antipsychotics could be predicted depending on the understanding of CYP or UGT isoenzymes responsible for their metabolism.

The suggested mechanism for the higher concentrations of these drugs in the plasma of the patients may be due to a lower hepatic clearance of these drugs or a decrease in hepatic metabolic function, a small liver volume, or a reduction in hepatic blood flow. Also, the demonstration of these drugs may cause upregulation or downregulation of the CYP or UGT mRNAs in hepatocytes by specific pathways, which will significantly induce or reduce their clinical effects.

Finally, it should be highlighted that adverse drug interactions in patients treated with antipsychotics may be decreased or prohibited by careful dosage regulations depending on the assessments of clinical response and plasma levels monitoring of the administrated antipsychotics. Olanzapine, quetiapine, and risperidone may share some common side effects. Therefore, combined use of them could increase the incidence and severity of specific side effects compared to use them separately.

3.4. Academic Contribution of This Study

In general, the use of antipsychotic medications, especially for children with autism, should be carefully considered. Benefits and risks must be accurately measured and studied case by case. Monitoring of plasma drug levels is recommended to ensure the best results and avoid adverse effects.

Available studies of such drugs in plasma related to given doses discuss the potential side effects in children. For example, risperidone [51] and olanzapine

[52] cause severe side effects such as weight gain. On the other hand, quetiapine has orthostatic hypertension as a side effect [53].

The novelty of this study is pointing out that in the Middle East there is a high demand and crucial need to monitor the drug concentration in plasma. This improves and optimizes the dose to achieve the best fixed dose for a patient. This study enriches the literature and assists people in charge, e.g., regulators, to make necessary decisions to overcome the side effects for autistic children for better life performance. As a result, the effectiveness of the treatment of autistic children will be enormously enhanced.

4. Conclusion

This study provided and discussed data for 18 children with ASD. Plasma was analyzed using LC-MS/MS to assess the levels of olanzapine, risperidone, and quetiapine medications

The results were argued against the recommended drug doses and their TDM concentrations in plasma. The reference was to take the steady-state concentration of the medications according to the amount.

The results showed that specific drug plasma concentrations are higher than those reported in the literature. These results conclude that the patients are taking their medications. Therefore, physicians are prescribing the medications drugs, which leads to the high possibility of side effects and adverse effects of the medicine DDI and food-drug interactions. These data must increase awareness between physicians and the medical field about the importance of finding a better-effective treatment for people affected by ASD, in addition to better-fixed doses of these medications.

Awareness campaigns should be established to educate parents about the importance of taking medication at the right time, including a proper dose. This way, a child will not consume less or more than the prescribed amount. A recommendation should be made where a pharmacist could draw physician to an overdosed prescribed drug. Also, the software can be used with warning limits of mg/day. A work check is a crucial tool for monitoring an adequate concentration of a drug in plasma throughout treatment.

Also, this data revealed the need for guidelines on therapeutic drug monitoring of antipsychotics for such patients who may have different drug absorption, distribution, metabolism, and elimination.

The future perspective to continue this study is to expand to several autism centers within Jordan and the Arab world. In addition, genetic mapping is planned to be applied to all the present and future autistic samples, and link them with LC/MS/MS results to investigate any correlations between them.

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Supplementary Material

S1 Children's blood work data

	Conventional Units	MEAN	Standard deviation
Uric acid	3.4-7.5 mg/dL	4.9	1.5
Urea	< 50 mg/dL	27	6.7
Creatinine	0.2-1 mg/dL	0.7	0.33
Sodium	135-153 mmol/L	146	3.5
Potassium	3.5-5.3 mmol/L	4.3	0.29
Chloride	97-111 mmol/L	106	5.1
Alanine aminotransferase, ALT	7-40 U/L	13	5.1
Aspartate aminotransferase, AST	(SGOT)/8-40 U/L	24	5.5
Gamma-glutamyl transferase, GGT	11-49 U/L	17	10.1
Alkaline phosphatase	< 460 U/L	146	73.3
Total protein	4.8-8.7 g/Dl	7.4	0.46
Albumin	3.5-5.1 g/dL	4.5	0.29
Globulin	2.0-3.5 g/dl	2.9	0.47
Bilirubin-total	Up to 1.00 mg/dL	0.59	0.26
Bilirubin- direct	Up to 0.25 mg/dL	0.12	0.042
Thyroid-stimulating hormone, TSH	0.4 - 4.5 mIU/mL	2.9	1.7
Triiodothyronine, Free T3	1.2-4.1 Pg/mL	3.1	0.38
Thyroxin, free T4	0.89-1.72 ng/dL	1.18	0.18
Ferritin	25-350 ng/mL/Child: 10-140	46.23	22.7
Vitamin B12	200-1100 Pg/mL	483.53	145.6
25-hydroxy vitamin D3 (nmol/L)	Deficient: < 25 Insufficient: 25-74 Sufficient: 75-250 Toxic: > 250	54.76	24.2

S2 Daily medication regimen

Daily Medications Regimen

1	Olanzapine 50 mg - 1×2/ Carbamazepine 200 mg - ½×2
2	Quetiapine 250 - 1×1/Risperidone 0.5 mg - 1×2/ Topiramate 25 mg - 2×2
3	Risperidone 2 mg - 1×2/ Carbamazepine 200 mg - ½×2 / Valproate 500 mg- ½×2
4	Risperidone 1 mg- 1×1/ Valproate- ½×2/
5	Olanzapine 10 mg - 1×1/ Risperidone 1 mg - 1×2/ Amisulpride 100 mg- 1×2/ Valproate 500 mg- 1×2
6	Risperidone 0.5 mg - 1×1
7	Risperidone 4 mg - 1×2/ Lamotrigine 50 mg - 1×2/ Carbamazepine 200 mg- 1×2
8	Olanzapine 5 mg - 1×1/ Valproate - 1×2
9	Quetiapine 100 mg - 1×2/ Amisulpride 50 mg - 1×1/ Amisulpride 100 mg- 1×2
10	Quetiapine 25 mg - 1×1/ Cyproterone 10 mg - 1×2/ Levetiracetam 250 mg- 1×1/ Valproate - ½×1
11	Olanzapine 10 mg - 1×2/ Risperidone 2 mg - 1×2/ Carbamazepine 200 mg- 1×1
12	Olanzapine 5 mg - 1×1/ Quetiapine XR 200 mg - 1×2/ Risperidone 0.5 mg - 1×1/ Propranolol 10 mg - 1×1/ Levetiracetam 500 mg - 1×1/ Topiramate 25 mg - 2×2/ Paliperidone 9 mg - 1×1
13	Quetiapine 50 mg - 1×1

