has been hypothesized for carbamazepine and oxcarbazepine.4

When a clear sequence of events is available, as in the present case, the risk of antipsychotics combined with carbamazepine/oxcarbazepine leading to SIADH or polydipsia19 should be seriously evaluated up-front, especially in a patient with genetic epilepsy who is at increased risk due to a supratherapeutic carbamazepine therapy. To prevent electrolyte imbalances, a cheap and feasible strategy comprises routine blood examinations, therapeutic drug monitoring, and the monitoring of patients’ water intake because polydipsia may be an important pathological marker. This grants the opportunity to detect subtle electrolyte changes that may otherwise go unnoticed until they have a clinically relevant impact. Proper monitoring should be always performed as a precaution because subclinical hyponatremia may also reduce neuropsychological performances.20

The present case is an example of how 2 drugs with a low-risk potential synergized to produce an adverse reaction. The risk of developing an ADR in this patient went unnoticed; because she never displayed polydipsia, detection of the ADR was virtually impossible without an accidental blood examination. Proper drug monitoring and knowledge of drug-specific risks of ADRs may prevent seizure precipitation due to electrolyte imbalances and should be encouraged as part of an optimal clinical practice.

AUTHOR DISCLOSURE INFORMATION
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Emilio Clementi, PhD
Scientific Institute IRCCS Eugenio Medea
Bosco Parini, Lecco, Italy and Unit of Clinical Pharmacology CNR Institute of Neuroscience Department of Biomedical and Clinical Sciences L. Sacco “Luigi Sacco” University Hospital Università di Milano, Milan, Italy
emilio.clementi@unimi.it

REFERENCES

Interaction Between Risperidone, Venlafaxine, and Metronidazole
An Unknown Thread

To the Editors:
When metronidazole (MET) was coprescribed to an ongoing pharmacological treatment, elevated plasma concentrations have been reported for a number of cytochrome CYP3A4 substrates including amiodarone, carbamazepine, cyclosporine, and others. The clinical significance of drug-drug interactions (DDIs) has been illustrated mostly by case reports.1,2 However, pharmacokinetic evidence does not support an inhibiting effect of MET on CYP3A4/5 activity.3 Alternatively, dose-dependent pharmacokinetic patterns may offer explanatory models for the discrepancy between case reports and in vivo studies.4 In vitro findings imply an inhibiting effect of MET on CYP2C9, but not on CYP2D6.5,6 However, the mechanism by which MET alters the disposition of different drugs including tacrolimus, amiodarone, cyclosporine, carbamazepine, and quinidine7 remains unclear so far; it might also be a result of its influence on transport proteins such as p-glycoprotein, although data do not support an inhibiting effect on p-glycoprotein hitherto.7,8 Hence,
DDIs between MET and a number of drugs have to be further elucidated because they may be the result of various processes including alterations in absorption, distribution, metabolism, and excretion of the affected drug. In addition, inflammatory conditions may be associated with CYP inhibition and particularly with an inhibition of risperidone (RIS) metabolism. Researchers suggested that the underlying mechanism might include inhibition and acetylation processes. In this regard, therapeutic drug monitoring (TDM) can be used to optimize patient-oriented pharmacotherapy helping to disentangle DDIs in clinical settings. Therefore, we report a clinically interesting case in which the addition of MET to an ongoing treatment with RIS and venlafaxine (VEN) led to an unexpected increase of the serum levels and a change in the relation between the parent compound and the metabolites (altering the so-called metabolic ratio) of both psychotropic drugs.

CASE REPORT

Mrs L is an 81-year-old inpatient diagnosed with a recurrent major depressive disorder with psychotic symptoms (ICD-10: F33.3) including delusion of poisoning. She was hospitalized in the Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital of Aachen, Germany, and was initially treated with nortriptyline 75 mg and RIS up to 2 mg. This was the therapeutic regimen at the time of admission. Because of a lack of response in the outpatient setting, VEN was started in daily dosages up to 187.5 mg, RIS dosage was increased up to 4 mg, and nortriptyline was stopped. The patient had been already under this therapeutic regimen for a week when she was diagnosed with a nosocomial infection of the urinary tract. Cefuroxime was added for an antimicrobial therapy. Hereafter, a Clostridium difficile-associated diarrhea occurred, and an antimicrobial therapy with MET in a daily dosage of 1,200 mg (in 400 mg tablets) was initiated, and routine examinations including TDM were performed regularly. The clinical condition was marked by exsiccosis and general exhaustion on the day when MET was started. The laboratory revealed a C-reactive protein (CRP) enhancement up to 70.2 mg/mL (reference range, <5 mg/mL) but normal leucocytes. Furthermore, starting from initially normal serum sodium levels, a hyponatremia with a level of 129 mmol/L (reference range, 136–145 mmol/L) occurred 2 days after the MET therapy initiation, whereas no changes in electrocardiogram results were observed (QT, 441 milliseconds). At this point, renal function parameters were normal.

Two weeks before the start of the antimicrobial treatment, the serum level for the so-called active moiety (AM) (sum of RIS + 9-hydroxyrisperidone [9-OH-RIS]) was 77.9 ng/mL and higher as the therapeutic reference range of 20 to 60 ng/mL. Although serum levels for both psychotropic drugs were very high, no signs of intoxication or severe adverse effects could be observed. Only the low blood pressure and intermittent nonveriginous dizziness, associated with headache, were clinically evident. Revealing the decrease in sodium serum levels and the high drug concentrations justified an adjustment of the therapeutic regimen, and the applied daily dosages were reduced. However, the patient was transferred to an internal ward because of continuing diarrhea. One week later, she was released home with the discharge diagnoses of clostridial enteritis and urinary tract infection caused by Pseudomonas aeruginosa. The discharge therapeutic regimen consisted of RIS 4 mg and VEN 75 mg. Aside from the psychopharmacological treatment, the patient received an antimicrobial therapy with vancomycin 750 mg.

### TABLE 1. Serum Concentrations of RIS and Its Metabolite 9-OH-RIS as well as Serum Concentrations of VEN and Its Metabolite ODV as Trough Levels

<table>
<thead>
<tr>
<th>Day (Start of MET on Day 0)</th>
<th>Before</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 10</th>
<th>Day 12</th>
<th>Day 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 17 CRP (mg/L)</td>
<td>42.0</td>
<td>42.3</td>
<td>32.1</td>
<td>21.0</td>
<td>18.3</td>
<td>60.4</td>
</tr>
<tr>
<td>Day 17 Albumin (g/dL)</td>
<td>np</td>
<td>np</td>
<td>np</td>
<td>np</td>
<td>np</td>
<td>np</td>
</tr>
<tr>
<td>Day 17 Total protein (g/dL)</td>
<td>np</td>
<td>np</td>
<td>np</td>
<td>np</td>
<td>np</td>
<td>np</td>
</tr>
<tr>
<td>Day 17 Blood creatinine (mg/L)</td>
<td>7.6</td>
<td>4.7</td>
<td>6.2</td>
<td>4.3</td>
<td>4.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Day 17 Creatinine clearance (mL/min/1.73 m²)</td>
<td>73.8</td>
<td>92.9</td>
<td>84.8</td>
<td>95.7</td>
<td>97.2</td>
<td>89.3</td>
</tr>
<tr>
<td>Day 17 DD RIS (mg)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Day 17 RIS (ng/mL)</td>
<td>2.5</td>
<td>17</td>
<td>28</td>
<td>18.9</td>
<td>39.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Day 17 9-OH-RIS (ng/mL)</td>
<td>75.4</td>
<td>173</td>
<td>197</td>
<td>171</td>
<td>137</td>
<td>88.4</td>
</tr>
<tr>
<td>Day 17 RIS + 9-OH-RIS (ng/mL)</td>
<td>77.9</td>
<td>190</td>
<td>225</td>
<td>189.9</td>
<td>176.6</td>
<td>96.7</td>
</tr>
<tr>
<td>Day 17 Ratio 9-OH-RIS/RIS</td>
<td>30.16</td>
<td>10.18</td>
<td>7.04</td>
<td>9.05</td>
<td>3.46</td>
<td>10.65</td>
</tr>
<tr>
<td>Day 17 DD VEN (mg)</td>
<td>75.0</td>
<td>187.5</td>
<td>187.5</td>
<td>187.5</td>
<td>150.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Day 17 VEN (ng/mL)</td>
<td>np</td>
<td>496</td>
<td>446</td>
<td>143</td>
<td>160</td>
<td>224</td>
</tr>
<tr>
<td>Day 17 ODV (ng/mL)</td>
<td>np</td>
<td>886</td>
<td>803</td>
<td>457</td>
<td>470</td>
<td>282.7</td>
</tr>
<tr>
<td>Day 17 VEN + ODV (ng/mL)</td>
<td>np</td>
<td>1,382</td>
<td>1,249</td>
<td>600</td>
<td>630</td>
<td>506.7</td>
</tr>
<tr>
<td>Day 17 Ratio, ODV/VEN</td>
<td>np</td>
<td>1.79</td>
<td>1.80</td>
<td>3.20</td>
<td>2.94</td>
<td>1.26</td>
</tr>
</tbody>
</table>

Because of the short interval between TDM measures and the long half-life of RIS and particular 9-OH-RIS, steady-state conditions (>5 half-life times) could not be established.

np indicates not performed.
and ciprofloxacin 1500 mg. Metronidazole had been already stopped when the patient was transferred to the internal ward.

**DISCUSSION**

The primary pathway of RIS metabolism is a CYP2D6-catalyzed 9-hydroxylolation, and the main active metabolite is 9-OH-RIS. Furthermore, in vitro findings have revealed that CYP3A4 and CYP3A5 might be also involved in the metabolism of RIS.13 Risperidone and 9-OH-RIS exhibit differences in 5-HT2A/D2 (serotonin/dopamine) binding ratios, show differences in plasma-protein binding (90% vs 74%) and in terminal half-life time (3 hours for RIS vs 23 hours for 9-OH-RIS). For RIS, 2 TDM measures have received particular attention14; the ratio RIS/9-OH-RIS is considered as a reliable measure of CYP2D6 metabolic activity, and the AM (RIS + 9-OH-RIS) divided by the RIS dosage ([VEN + ODV]/D) in [ng/mL]/[mg/d]) should provide a reasonable measure of the drugs' serum levels. Knowledge of the cytochrome system do not sufficiently account for the increase of drug concentrations of RIS, 9-OH-RIS, VEN, and ODV after the addition of MET. Moreover, there were no hints of renal impairment. Therefore, it remains unclear why, in the case of 9-OH-RIS and ODV, the patient was not able to eliminate the metabolites. It might be seen as a complex pharmacokinetic interaction and/or the consequence of the inflammatory condition. Nevertheless, in our case, an inhibitory effect of inflammation is not clearly demonstrated because the temporal course of CRP values did not match the course of the drugs' serum levels. Knowledge of CYP2D6 and CYP2C19 genotypes would undoubtedly shed light on the mechanism underpinning the interaction reported here. However, genetic tests of CYP activity for polymorphic cytochrome enzymes are still not established in clinical routine, and this option was not available in our case hampering a better understanding of this evidence.

Our case underscores the usefulness of TDM for treatment optimization and improvement of patients' safety. Luckily, except orthostatic hypotension and dizziness, no other clinically relevant adverse effects could be observed. The mentioned undesirable effects partly subsided after reducing the daily dosage of RIS and VEN. Our case report highlights the benefits of TDM application in clinical routine as an alarm for individual abnormalities such as DDIs essentially helping to prevent negative outcomes.

**AUTHOR DISCLOSURE INFORMATION**

Gerhard Gründer has served as a consultant for Boehringer Ingelheim (Ingelheim, Germany), Cheplapharm (Greifswald, Germany), Eli Lilly (India-napolis, Ind), Lundbeck (Copenhagen, Denmark), Ono Pharmaceuticals (Osaka, Japan), Roche (Basel, Switzerland), Servier (Paris, France), and Takeda (Osaka, Japan).

He has served on the speakers' bureau of Eli Lilly; Geleon Richter (Budapest, Ungarn); Janssen Cilag (Neuss, Germany); Lundbeck, Roche, Servier, and Trommsdorf (Aachen, Germany). He has received grant support from Boehringer Ingelheim and Roche. He is co-founder of Pharma Imaging GmbH (Düsseldorf, Germany) and Brainfoods UG (Selfkant, Germany). The other authors declare no conflicts of interest.

Jana Hovancakova, MD
Department of Psychiatry
Psychotherapy and Psychosomatics
RWTH Aachen University
Aachen, Germany
and JARA – Translational Brain Medicine

Georgios Schortsanitis, MD
Department of Psychiatry
Psychotherapy and Psychosomatics
RWTH Aachen University
Aachen, Germany
and JARA – Translational Brain Medicine

Michael Grözinger, MD
Gerhard Gründer, MD
Michael Paulzen, MD
Department of Psychiatry
Psychotherapy and Psychosomatics
RWTH Aachen University
Aachen, Germany
and JARA – Translational Brain Medicine

**REFERENCES**


**Olanzapine Long-Acting Injections After Neuroleptic Malignant Syndrome Two Case Reports**

To the Editors:

Neuroleptic malignant syndrome (NMS) is a rare, unpredictable, but potentially life-threatening condition associated with antipsychotic use. It is characterized by rigidity, tremor, fever, alterations of mental status, leukocytosis, and creatine kinase (CK) elevation. Although more than half of all reported NMS cases are associated with haloperidol, it is associated with virtually all antipsychotics. Patients with schizophrenia need to be treated after recovery from NMS, but they are at an elevated risk of developing NMS after future exposure to antipsychotics. The data regarding antipsychotic treatment after NMS are sparse. Low-potency antipsychotics are recommended, including clozapine and quetiapine. Both drugs are available only in oral formulations. Long-acting injectable (LAI) antipsychotics are recommended for nonadherent patients with schizophrenia, and they showed superior compared with oral antipsychotics in preventing hospitalizations. There are no data of treatment with LAI antipsychotics after the resolution of NMS, and sustained high level of dopamine D2 receptor occupancy might induce the recurrence of NMS. Olanzapine LAI was associated with D2 receptor occupancy of approximately 60%. Other LAI antipsychotics including haloperidol decanoate and risperidone LAI occupy a higher percentage of dopamine D2 receptors. There are currently no data for paliperidone and aripiprazole LAIs.

Given that olanzapine was recommended as a safe and effective option after NMS and the relatively low occupancy of dopamine D2 receptors with olanzapine LAI, we present 2 patients, known to be nonadherent with antipsychotics, who were treated with olanzapine LAI after the resolution of NMS.

In both patients, diagnosis of schizophrenia and NMS was established according to criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (published by the American Psychiatric Press, 1994).

**CASE REPORTS**

**Case 1**

A 37-year-old man was given a diagnosis of schizophrenia 15 years ago and had several episodes of nonadherence to his treatment regimen. For the previous 7 years, he received the combination of risperidone LAI 25 mg every 2 weeks and clozapine 50 mg in the evening. He was in remission for the last 6 years. However, his condition worsened 2 weeks before admission, and the patient was given aripiprazole 10 mg daily. Ten days later, he was hospitalized because of stupor, mutism, and the loss of contact. Soon after, he developed fever (highest temperature, 39.2°C), tremor, intensive perspiration, elevated CK (highest value, 1473 U/L; reference range, 0–177 U/L), altered consciousness, tachycardia (highest rate, 123), dysarthria, and dysphagia. Antipsychotics were discontinued, and she was transferred to the intensive care unit where she stayed for 2 weeks. Although fever resolved and CK levels normalized, the patient developed catatonia, presenting with negativism, mutism, and occasional episodes of uncontrolled motor restlessness. She was admitted in our department for electroconvulsive therapy, where she received 12 applications and her condition improved. In addition, oral olanzapine was started, with slow and careful titration up to 20 mg daily. Because treatment with olanzapine was both safe and effective and the risk of nonadherence was high, olanzapine LAI 300 mg twice monthly was instituted. The patient has been receiving olanzapine LAI at the same dose for 15 months, with 10 mg of oral olanzapine twice daily and 1500 mg of valproate to treat occasional mood swings. Functional remission is achieved, and the patient is working full time. Olanzapine concentration was 323.1 nmol/mL before LAI injection and 251.0 nmol/mL 3 hours after the most recent injection (reference range, 64–256 nmol/mL). However, the patient received oral olanzapine at 7:00 AM, and the first sample was taken at 1:00 PM. This corresponds to maximal concentration after oral olanzapine intake.

**Case 2**

A 37-year-old man was given a diagnosis of schizophrenia 15 years ago and had several episodes of nonadherence to his treatment regimen. For the previous 7 years, he received the combination of risperidone LAI 25 mg every 2 weeks and clozapine 50 mg in the evening. He was in remission for the last 6 years. However, his condition worsened 2 weeks before admission, and the patient was given aripiprazole 10 mg daily. Ten days later, he was hospitalized because of stupor, mutism, and the loss of contact. Soon after, he developed fever (highest temperature, 39.2°C), tremor, intensive perspiration, elevated CK (highest value, 1473 U/L; reference range, 0–177 U/L), altered consciousness, tachycardia (highest rate, 123), dysarthria, and dysphagia. Antipsychotics were discontinued, and she was transferred to the intensive care unit where she stayed for 2 weeks. Although fever resolved and CK levels normalized, the patient developed catatonia, presenting with negativism, mutism, and occasional episodes of uncontrolled motor restlessness. She was admitted in our department for electroconvulsive therapy, where she received 12 applications and her condition improved. In addition, oral olanzapine was started, with slow and careful titration up to 20 mg daily. Because treatment with olanzapine was both safe and effective and the risk of nonadherence was high, olanzapine LAI 300 mg twice monthly was instituted. The patient has been receiving olanzapine LAI at the same dose for 15 months, with 10 mg of oral olanzapine twice daily and 1500 mg of valproate to treat occasional mood swings. Functional remission is achieved, and the patient is working full time. Olanzapine concentration was 323.1 nmol/mL before LAI injection and 251.0 nmol/mL 3 hours after the most recent injection (reference range, 64–256 nmol/mL). However, the patient received oral olanzapine at 7:00 AM, and the first sample was taken at 1:00 PM. This corresponds to maximal concentration after oral olanzapine intake.