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 polydipsia[19] should be seriously evaluated upfront, 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

Dr Clementi has received funding from Agenzia Italiana del Farmaco (AIFA) and the Italian Ministry of Health (Ricerca Corrente 2016). The funding public institutions had no role in any part of the work. The other authors have no financial interests to declare.

Marco Pozzi, PhD
Scientific Institute IRCCS Eugenio Medea
Bosisio Parini, Lecco, Italy

Roberta Pineschi, MD
Associazione La Nostra Famiglia
Presidio di Riabilitazione
di Treviso
Treviso, Italy

Paolo Bonanni, MD
Epilepsy and Clinical
Neurophysiology Unit
Scientific Institute IRCCS
Eugenio Medea
Conegliano, Treviso, Italy

Alda Pellegri, MD
Scientific Institute IRCCS Eugenio Medea
Bosisio Parini, Lecco, Italy

Emilio Clementi, PhD
Scientific Institute IRCCS Eugenio Medea
Bosisio 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

1. Pisani F, Oteri G, Costa C, et al. Effects of psychotropic drugs on seizure threshold. *Drug Saf*. 2002;25:91–110.
2. Hedges D, Jeppson K, Whitehead P. Antipsychotic medication and seizures: a review. *Drugs Today (Barc)*. 2003;39: 551–557.
3. Van Amelsvoort T, Bakshi R, Devaux CB, et al. Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review. *Epilepsia*. 1994;35:181–188.
4. Mavragani CP, Vlachoyiannopoulos PG. Is polydipsia sometimes the cause of oxcarbazepine-induced hyponatremia? *Eur J Intern Med*. 2005;16:296–297.
5. Goldman MB. The assessment and treatment of water imbalance in patients with psychosis. *Clin Schizophr Relat Psychoses*. 2010;4:115–123.
6. Castilla-Guerra L, del Carmen Fernández-Moreno M, López-Chozas JM, et al. Electrolytes disturbances and seizures. *Epilepsia*. 2006;47:1990–1998.
7. Bartter FC. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *Dis Mon*. 1973;19:1–47.
8. Lee YF, Tsai CK, Liang CS. High-dose risperidone induced latent syndrome of inappropriate antidiuretic hormone secretion with seizure presentation. *Clin Neuropharmacol*. 2015;38:154–155.
9. Meulendijks D, Mannesse CK, Jansen PA, et al. Antipsychotic-induced hyponatraemia: a systematic review of the published evidence. *Drug Saf*. 2010;33:101–114.
10. Bachu K, Godkar D, Gasparyan A, et al. Aripiprazole-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH). *Am J Ther*. 2006;13:370–372.
11. de Bragança AC, Moyses ZP, Magaldi AJ. Carbamazepine can induce kidney water absorption by increasing aquaporin 2 expression. *Nephrol Dial Transplant*. 2010;25:3840–3845.
12. Kuz GM, Manssourian A. Carbamazepine-induced hyponatremia: assessment of risk factors. *Ann Pharmacother*. 2005;39:1943–1946.
13. Dibbens LM, Tarpey PS, Hynes K, et al. X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. *Nat Genet*. 2008;40: 776–781.
14. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry*. 2011;44:195–235.
15. Vieweg WV, Leadbetter RA. Polydipsia-hyponatraemia syndrome: epidemiology, clinical features and treatment. *CNS Drugs*. 1997;7:121–138.
16. Duraiswamy K, Rao NP, Venkatasubramanian G, et al. Psychogenic polydipsia in bipolar affective disorder—a case report. *Gen Hosp Psychiatry*. 2011;33:e9–e10.
17. Rao N, Venkatasubramanian G, Korpade V, et al. Risperidone treatment for polydipsia and hyponatremia in schizophrenia: a case report. *Turk Psikiyatri Derg*. 2011;22: 123–125.
18. Bersani G, Pesaresi L, Orlandi V, et al. Atypical antipsychotics and polydipsia: a cause or a treatment? *Hum Psychopharmacol*. 2007;22: 103–107.
19. Atsariyasing W, Goldman MB. A systematic review of the ability of urine concentration to distinguish antipsychotic- from psychosis-induced hyponatremia. *Psychiatry Res*. 2014;217:129–133.
20. Decaux G. Is asymptomatic hyponatremia really asymptomatic? *Am J Med*. 2006;119: S79–S82.

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 *CYP3A* 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 quinidine[3] 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[9] and particularly with an inhibition of risperidone (RIS) metabolism.[10,11] Researchers suggested that the underlying mechanism might include *CYP3A4*, glucuronosyltransferases, or drug efflux transporters.[10] 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_C 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.[12] Nonetheless, the daily dosage of 4 mg remained unchanged. At this moment, it had been only 3 days after initiation of VEN therapy and daily dosage was low; thereby, TDM did not include VEN. After starting the MET treatment (on day 0), serum levels of the AM were raised up to 225 ng/mL (Table 1) and exceeded the upper threshold of the therapeutic reference range nearly fourfold. Serum concentrations of VEN and O-desmethylvenlafaxine (ODV) were found to be unusually high after starting MET. The AM (VEN + ODV) was found to be 1382 ng/mL and exceeded the upper threshold of the therapeutic reference range for VEN (100–400 ng/mL) more than threefold.[12] 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 nonvertiginous 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

		Concomitant Treatment With MET				
Day (Start of MET on Day 0)	**Before**	**Day 5**	**Day 6**	**Day 10**	**Day 12**	**Day 17**
CRP (mg/L)	42.0	42.3	32.1	21.0	18.3	60.4
Albumin (g/dL)	np	np	np	np	np	1.9
Total protein (g/dL)	np	np	np	np	4.1	4.1
Blood creatinine (mg/L)	7.6	4.7	6.2	4.3	4.1	5.3
Creatinine clearance (mL/min/1.73 m^2)	73.8	92.9	84.8	95.7	97.2	89.3
DD RIS (mg)	4	4	4	4	2	2
RIS (ng/mL)	2.5	17	28	18.9	39.6	8.3
9-OH-RIS (ng/mL)	75.4	173	197	171	137	88.4
RIS + 9-OH-RIS (ng/mL)	77.9	190	225	189.9	176.6	96.7
Ratio 9-OH-RIS/RIS	30.16	10.18	7.04	9.05	3.46	10.65
DD VEN (mg)	75.0	187.5	187.5	187.5	150.0	75.0
VEN (ng/mL)	np	496	446	143	160	224
ODV (ng/mL)	np	886	803	457	470	282.7
VEN + ODV (ng/mL)	np	1382	1249	600	630	506.7
Ratio, ODV/VEN	np	1.79	1.80	3.20	2.94	1.26

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-hydroxylation, 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-HT_{2A}/D_2 (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 attention[14]; 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 (total concentration-by-dose ratio in [ng/mL]/[mg/d]) is considered to sufficiently reflect the total clearance of RIS. If the latter is increased in the absence of an increase in RIS/9-OH-RIS, it may be a sign of *CYP3A4* inhibition. Venlafaxine is principally metabolized not only by *CYP2D6* to ODV, its major active metabolite, but also by *CYP3A4* to the inactive metabolite N-desmethylvenlafaxine, and, to some degree, *CYP2C19* and *CYP2C9* play a role in the metabolism of VEN too. When comparing VEN with other antidepressants, it is reported to show a low protein binding (27% for VEN and 30% for ODV).[15] Of clinical interest are the differences between VEN and ODV regarding their half-life (5 and 11 hours) as well as renal excretion (5% and 30%).[16] The ratio ODV to VEN provides valuable information for the metabolizer status,[17] whereas the total ODV + VEN concentration divided by VEN dosage ([{VEN + ODV}/D] in [ng/mL]/[mg/d]) should provide a reasonable measure of total VEN clearance[12] as the so-called dose-adjusted plasma or serum concentration. There is a previously described pharmacokinetic interaction between VEN and RIS via *CYP2D6* because VEN is a weak inhibitor of 2D6 leading to higher concentrations of RIS and to a decrease in renal elimination of 9-OH-RIS.[18]

The metabolism of MET is independent from *CYP2D6* activity,[19] and the main metabolic pathway involves *CYP2A6*. No pharmacokinetic interactions between MET and RIS or MET and VEN are previously described. Of specific interest is the spectacular increase in blood levels and particularly active metabolites of both psychotropic drugs; this implies an effect of MET on both drugs rather than a cascade of pharmacokinetic changes. However, pharmacokinetic interactions via 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 (Indianapolis, 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, Gedeon 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 cofounder of Pharma Image 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 Schoretsanitis, MD
Department of Psychiatry
Psychotherapy and Psychosomatics
RWTH Aachen University
Aachen, Germany
and JARA –
Translational Brain Medicine
and Translational Research Center
University Hospital of Psychiatry
Bern, Switzerland
george.schor@gmail.com

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

1. Page RL 2nd, Klem PM, Rogers C. Potential elevation of tacrolimus trough concentrations with concomitant metronidazole therapy. *Ann Pharmacother*. 2005;39:1109–1113.
2. Kounas SP, Letsas KP, Sideris A, et al. QT interval prolongation and torsades de pointes due to a coadministration of metronidazole and amiodarone. *Pacing Clin Electrophysiol*. 2005; 28:472–473.
3. Roedler R, Neuhauser MM, Penzak SR. Does metronidazole Interact with CYP3A substrates by inhibiting their metabolism through this metabolic pathway? Or should other mechanisms be considered? *Ann Pharmacother*. 2007;41:653–658.
4. Dilger K, Fux R, Rock D, et al. Effect of high-dose metronidazole on pharmacokinetics of oral budesonide and vice versa: a double drug interaction study. *J Clin Pharmacol*. 2007; 47:1532–1539.
5. Obach RS, Walsky RL, Venkatakrishnan K, et al. The utility of in vitro cytochrome P450 inhibition data in the prediction of drug-drug interactions. *J Pharmacol Exp Ther*. 2006;316: 336–348.
6. Levy RH. Cytochrome P450 isozymes and antiepileptic drug interactions. *Epilepsia*. 1995; 36(Suppl 5):8–13.
7. Kim KA, Park JY. Effect of metronidazole on the pharmacokinetics of fexofenadine, a P-glycoprotein substrate, in healthy male volunteers. *Eur J Clin Pharmacol*. 2010;66: 721–725.
8. Wang JS, Backman JT, Kivistö KT, et al. Effects of metronidazole on midazolam metabolism in vitro and in vivo. *Eur J Clin Pharmacol*. 2000; 56:555–559.
9. Shah RR, Smith RL. Inflammation-induced phenoconversion of polymorphic drug metabolizing enzymes: hypothesis with implications for personalized medicine. *Drug Metab Dispos*. 2015;43:400–410.

10. Hefner G, Falter T, Bruns K, et al. Elevated risperidone serum concentrations during acute inflammation, two cases. *Int J Psychiatry Med*. 2015;50:335–344.
11. Hefner G, Shams ME, Unterecker S, et al. Inflammation and psychotropic drugs: the relationship between C-reactive protein and antipsychotic drug levels. *Psychopharmacology (Berl)*. 2016;233:1695–1705.
12. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry*. 2011;44:195–235.
13. Fang J, Bourin M, Baker GB. Metabolism of risperidone to 9-hydroxyrisperidone by human cytochromes P450 2D6 and 3A4. *Naunyn Schmiedebergs Arch Pharmacol*. 1999;359: 147–151.
14. Spina E, de Leon J. Clinical applications of CYP genotyping in psychiatry. *J Neural Transm (Vienna)*. 2015;122:5–28.
15. Preskorn SH. Pharmacokinetics of antidepressants: why and how they are relevant to treatment. *J Clin Psychiatry*. 1993;54(Suppl): 14–34 discussion 55-16.
16. Klamerus KJ, Maloney K, Rudolph RL, et al. Introduction of a composite parameter to the pharmacokinetics of venlafaxine and its active O-desmethyl metabolite. *J Clin Pharmacol*. 1992;32:716–724.
17. Preskorn SH, Kane CP, Lobello K, et al. Cytochrome P450 2D6 phenoconversion is common in patients being treated for depression: implications for personalized medicine. *J Clin Psychiatry*. 2013;74:614–621.
18. Amchin J, Zarycranski W, Taylor KP, et al. Effect of venlafaxine on the pharmacokinetics of risperidone. *J Clin Pharmacol*. 1999;39: 297–309.
19. Pearce RE, Cohen-Wolkowiez M, Sampson MR, et al. The role of human cytochrome p450 enzymes in the formation of 2-hydroxymetronidazole: CYP2A6 is the high affinity (low km) catalyst. *Drug Metab Dispos*. 2013;41:1686–1694.

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.[1] Although more than half of all reported NMS cases are associated with haloperidol, it is associated with virtually all antipsychotics.[2] 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[3] and quetiapine.[1,3] Both drugs are available only in oral formulations. Long-acting injectable (LAI) antipsychotics are recommended for nonadherent patients with schizophrenia, and they showed superiority compared with oral antipsychotics in preventing hospitalizations.[4] 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%.[5] Other LAI antipsychotics including haloperidol decanoate and risperidone LAI[6,7] 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[8] and the relatively low occupancy of dopamine D2 receptors with olanzapine LAI,[5] 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 30-year-old woman has been treated for schizophrenia for 9 years. She had several episodes of nonadherence to medication. For the last 3 years, she was receiving risperidone LAI 50 mg twice monthly, combined with oral risperidone 4 mg daily. Because the patient was in good remission, oral risperidone was withdrawn. Several months before admission, she was receiving only risperidone LAI, twice monthly. Despite regular applications, her condition worsened in terms of agitation, paranoid delusions, insomnia, and disorganized thinking and behavior, resulting in emergency hospitalization. Upon admission, short-acting muscular haloperidol was applied, followed by oral haloperidol 15 mg daily for the next 9 days. For the next 6 days, haloperidol dose was reduced to 6 mg daily, and risperidone was instituted at the dose of 6 mg daily. The patient developed fever (highest temperature, 38.6°C), muscular rigidity, tremor, elevated CK levels (highest value, 3486 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/L before LAI injection and 251.0 nmol/L 3 hours after the most recent injection (reference range, 64–256 nmol/L). 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), muscular rigidity, tachycardia (highest value, 105), tachypnea, leukocytosis (highest value, 15.2), incontinence, and dehydration. He was treated in the intensive care unit, and although somatic symptoms were resolved during the next 4 days, the patient was still in stupor. He received 11 applications of electroconvulsive therapy. His condition gradually recovered,