**Supplementary Table S1 – Carbamazepine pharmacokinetics**

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| --- |
| *Metabolism* |
| • Carbamazepine is primarily metabolized by CYP3A4 (with a minor contribution from CYP2C8) to its active metabolite, 10,11-epoxide. While this may account for 40% of carbamazepine metabolism, the proportion is even greater in patients with induced CYP3A4, which is probably most if not all patients, since carbamazepine is a potent inducer of CYP3A44,5 |
| • Other pathways: – Aromatic hydroxylation (25%), possibly by CYP1A2 – Glucuronidation of the carbamoyl side chain by the UGTs, presumably by UGT2B76 |
| *Role as inducer* |
| • Carbamazepine is a potent inducer of multiple metabolic pathways, including several CYPs and several UGTs |
| • The consequence of carbamazepine inducing its own metabolism three-fold4 is that this drug may not reach steady state for the first 3-5 weeks due to the progressive increase in auto-induction7 |
| • Carbamazepine DDIs with psychiatric drugs8 have not been systematically studied for many psychiatric drugs |
| • Carbamazepine’s inductive effects on diazepam, quetiapine and risperidone are probably explained by CYP3A4 induction. However, the inductive effects may also be explained by p-glycoprotein (P‑gp) induction. There is limited understanding of the role of P‑gp in the metabolism of psychiatric drugs9 |
| • While there are no comprehensive studies describing the duration of the effect of carbamazepine or other potent CYP3A4 inducers (e.g., phenytoin), it is believed that the inductive effects generally disappear after 3 weeks of stopping the inducer10 |
| *TDM and C/D ratio*  |
| • Therapeutic concentration range:  – For epilepsy: 4-12 μg/mL7 – As a mood stabilizer: 4-10 μg/mL11 |
| • Carbamazepine maintenance dosing is usually established by TDM after reaching steady state. The *Drug Information Handbook* of the American Pharmacist Association describes the typical maximum recommended carbamazepine dose as up to 1600 mg/day, but some patients may require up to 2400 mg/day12 |
| • Very few published articles provide carbamazepine C/D ratios in adult patients. In 70 Iranian patients, Namazi et al.13 described a mean ± SD carbamazepine C/D ratio of 0.01±0.006 μg/mL/mg/day |

C/D: concentration-to-dose; CYP: cytochrome P450; CYP1A2: CYP isoenzyme 1A2; CYP2C8: CYP isoenzyme 2C8; CYP3A4: CYP isoenzyme 3A4; DDI: drug-drug interaction; SD: standard deviation; TDM: therapeutic drug monitoring; UGT: uridine 5’-diphospho-glucuronosyltransferase; UG2B7T: UGT isoenzyme 2B7.

**Supplementary Table S2 – Diazepam pharmacokinetics**

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| *Metabolism* |
| • Two major pathways14: – N-desmethylated by CYP2C19 and CYP3A4 to the active metabolite N‑desmethyldiazepam – Hydroxylated by CYP3A4 to the active metabolite temazepam |
| • N-desmethyldiazepam and temazepam are further metabolized to oxazepam |
| • Temazepam and oxazepam are largely eliminated by UGTs |
| • The relevance of CYP2C19 and CYP3A4 fluctuates based on:  – Dosage:15 CYP3A4 has lower affinity for diazepam: · In typical doses, diazepam is mainly metabolized by CYP2C19  · At higher diazepam doses: the relative contribution of CYP3A4 ↑ – CYP2C19 polymorphism: · PMs do not have CYP2C19 (20% of East Asians and <5% of Caucasian and Black populations):16 diazepam is probably mainly metabolized by CYP3A4 – Intake of CYP3A4 inducers: CYP3A4 may have a greater role than CYP2C19  |
| *TDM and C/D ratio* |
| • There is very limited information on diazepam TDM4 |
| • Therapeutic concentration range:  – For status epilepticus using IV diazepam: 200-800 ng/mL17  – As an anxiolytic drug: 200–2500 ng/mL including diazepam and its metabolites11 |
| • Total C/D ratio (the total C: sum of diazepam and nordiazepam): – Bond et al.:18 44 ng/mL/mg/day in 19 patients taking 11 mg/day  – Rutherford et al.:19 44-93 ng/mL/mg/day in 3 patients taking 30 mg/day  |

C: concentration; C/D: concentration-to-dose; CYP: cytochrome P450; CYP2C19: CYP isoenzyme 2C19; CYP3A4: CYP isoenzyme 3A4; IV: intravenous; TDM: therapeutic drug monitoring; UGT: uridine 5’-diphospho-glucuronosyltransferase; UG2B7T: UGT isoenzyme 2B7.

**Supplementary Table S3 – Quetiapine pharmacokinetics**

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| *Metabolism* |
| • In vitro study20: – CYP3A4: major metabolic pathway for quetiapine  – CYP2D6 and CYP2C9: minor contributors  |
| *Metabolism during treatment with inducers* |
| • CYP3A4 is one of the CYPs most sensitive to induction9 As quetiapine is mainly metabolized by CYP3A4, quetiapine is extremely sensitive to induction21 |
| • Carbamazepine effects: – In a prospective pharmacokinetic study of 18 patients, carbamazepine was titrated up during a 5-day period and kept at a dose of 600 mg/day for 11 days, which increased oral clearance of quetiapine 7.5-fold21 – Similar results have been seen in TDM studies,22‑25 which have been summarized by Spina et al.26 – Furthermore, the clinical implications of adding carbamazepine to quetiapine were demonstrated in 3 patients taking carbamazepine at doses of 400-800 mg/day, in which serum quetiapine concentrations could not be detected (<25 ng/mL), despite taking 700 mg/day27 |
| • Phenytoin ↑ quetiapine clearance 5-fold, requiring a 5-fold dosage increase26 |
| *TDM and C/D ratio* |
| • Therapeutic concentration range: 100-500 ng/ml11 |
| • With typical doses, quetiapine has a linear relationship between dose and concentration |
| • C/D ratio: very limited information has been published on how to use quetiapine C/D ratios to interpret quetiapine TDM. The multi-center studies conducted by the company29,30 did not describe C/D ratios but can be used to calculate them:  – Trough C29: ranged from 0.13-0.19 ng/ml/mg/day · 0.19 ng/ml/mg/day = 13 ng/ml/75 mg/day\*  · 0.19 ng/ml/mg/day = 27.8 ng/ml/150 mg/day\* · 0.15 ng/ml/mg/day = 43.9 ng/ml/300 mg/day\* · 0.15 ng/ml/mg/day = 91.1 ng/ml/600 mg/day\*  · 0.13 ng/ml/mg/day = 93.7 ng/ml/750 mg/day\*  – Peak C (1-1.5 hours)30: approximately 10 times higher; ranged from 1.0 to 1.4 ng/ml/mg/day · 1.2 ng/ml/mg/day = 277 ng/ml/225 mg/day in men (1.3 ng/ml/mg/day = 286 ng/ml/225 mg/day in women)\*  · 1.4 ng/ml/mg/day = 625 ng/ml/450 mg/day in men (1.3 ng/ml/mg/day = 572 ng/ml/450 mg/day in women)\* · 1.0 ng/ml/mg/day = 778 ng/ml/750 mg/day in men (1.2 ng/ml/mg/day = 879 ng/ml/750 mg/day in women)\* |
| • Fluctuations during the day between trough and peak Cs are due to the short half-life of quetiapine |

C: concentration; C/D: concentration-to-dose; CYP: cytochrome P450; CYP3A4: CYP isoenzyme 3A4; D: dose; TDM: therapeutic drug monitoring.

\*The C provided by each D is used to calculate C/D ratio (e.g., with D=75 mg/day the C=13 ng/ml provides a trough C/D ratio=0.19 ng/ml/mg/day).

**Supplementary Table S4 – Risperidone pharmacokinetics**

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| --- |
| *Metabolism* |
| • CYP2D6: The marketer proposed that risperidone is metabolized to the active metabolite 9-hydroxyrisperidone by CYP2D6. According to the company, the CYP2D6 polymorphism has no clinical relevance. CYP2D6 PMs (7% of Caucasians and <3% in other races) who do not have CYP2D6 do not have problems with risperidone metabolism. On the other hand, later studies have proposed that CYP2D6 PM status may decrease risperidone clearance31 |
| • CYP3A4 is also important for risperidone metabolism: – This was first proposed in a case report in which serum risperidone active moiety (risperidone and its pharmacologically active metabolite 9-hydroxyrisperidone) doubled after carbamazepine discontinuation, leading to an ADR32 – Other DDI studies verified that carbamazepine induces risperidone metabolism33‑36 – Finally, an in vitro study verified that risperidone is metabolized by CYP2D6 and CYP3A437 |
| *Metabolism during CYP3A4 induction* |
| • Although risperidone articles usually describe CYP2D6 as the main metabolic pathway for risperidone, in situations of induction, such as taking therapeutic doses of carbamazepine or phenytoin, it is possible that there is a substantial increase of CYP3A4 expression and CYP3A4 becomes the most important metabolic enzyme for risperidone38,39 |
| • After adding therapeutic doses of phenytoin or carbamazepine, it is necessary to duplicate risperidone D to keep the same C8 |
| *TDM and C/D ratio* |
| • Therapeutic concentration range: 20-60 ng/ml after adding risperidone and 9‑hydroxyrisperidone11 |
| • The risperidone C/D ratio: – Is calculated by dividing the total C (risperidone and 9-hydroxyrisperidone in ng/ml) by the D (mg/day) – Is interpreted as an index of total ability to eliminate risperidone by using CYP2D6, CYP3A4 and renal excretion – Has normal values around 7 ng/ml/mg/day31,39 – Decreases by half (<3.5 ng/ml/mg/day) in patients taking potent CYP3A4 inducers31,39 |

ADR: adverse drug reaction; C: concentration; C/D: concentration-to-dose ratio; CYP: cytochrome P450; CYP2D6: CYP isoenzyme 2D6; CYP3A4: CYP isoenzyme 3A4; D: dose; DDI: drug-drug interaction; PM: poor metabolizer; TDM: therapeutic drug monitoring.

**Supplementary Table S5 – Paliperidone pharmacokinetics**

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| --- |
| *Metabolism* |
| • Paliperidone is 9-hydroxyrisperidone, risperidone’s main metabolite, and was marketed after oral risperidone had lost its patent |
| • The company published a study of paliperidone metabolism in 5 male volunteers who were given 1 mg of paliperidone labelled with isotopes.40 In this study, approximately 60% of the compound was eliminated unchanged in the urine and the percentages were similar in subjects who were CYP2D6 PMs. Four paliperidone metabolic pathways were identified, each of which accounted for up to a maximum of 6.5% of the biotransformation of the total dose. The authors concluded that paliperidone is not extensively metabolized and is primarily excreted through the kidneys40 |
| • A comparative review written by the company researchers provided a more accurate description of this isotope paliperidone study.41 Metabolism of paliperidone accounts for 20% of elimination since 20% of it may be eliminated changed in the urine in the average non-induced subject. A review proposed that 20% of paliperidone being metabolized in non-induced subjects is not consistent with being “minimally metabolized”42 |
| *Metabolism during CYP3A4 induction* |
| • For years, based on his experience with risperidone,31,42,43 the senior author had hypothesized that risperidone’s main metabolite, one which, according to the marketer, was not supposed to be metabolized, may be quite susceptible to induction |
| • Paliperidone’s pharmaceutical company conducted a study to assess the effect of carbamazepine on paliperidone metabolism in healthy subjects, but the study used subtherapeutic doses of 400 mg/day, for 3 weeks, which is not enough to cause maximal CYP3A4 induction. In these circumstances, only a 37% decrease in paliperidone AUC was seen44 |
| • Yasui-Furakori et al.45 reported that 600 mg/day of carbamazepine for 2-4 weeks was associated with an average reduction in plasma paliperidone C to 1/3. This would require multiplying the paliperidone D by 3 in these patients26 |
| • It is possible that an even higher paliperidone D correction factor would be needed in patients taking higher carbamazepine doses or for longer periods of time |
| *TDM and C/D ratio* |
| • Therapeutic concentration range: 20-60 ng/ml after adding risperidone and 9‑hydroxyrisperidone11 |
| • Paliperidone C/D ratio: – In a TDM study with 217 German patients, the mean ± SD paliperidone C/D ratio was 4.7±2.9 ng/ml/mg/day46 – In 6 Japanese patients, Yasui-Furakori et al.45 found:  · A mean C/D ratio of 6.0 ng/ml/mg/day · decreased to 2.0 ng/ml/mg/day when carbamazepine was progressively added up to 600 mg/day for 2-4 weeks; this ↓ in serum paliperidone Cs was associated with psychotic exacerbations in some patients |

AUC: area under the curve; C: concentration; C/D: concentration-to-dose; CYP: cytochrome P450; CYP2D6: CYP isoenzyme 2D6; D: dose; PM: poor metabolizer; SD: standard deviation; TDM: therapeutic drug monitoring.

**Supplementary Table S6 – Olanzapine pharmacokinetics**

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| *Metabolism*47 |
| • Olanzapine is mainly metabolized by – N-demethylation, mediated by CYP1A2 and  – Direct N-glucuronidation, mediated by UGT1A4 |
| • Minor metabolic pathways are  – N-oxidation, catalyzed by the flavin-containing mono-oxygenase-3 system, and  – 2-hydroxylation, metabolized by CYP2D6 |
| • Thus, CYP3A4 does not appear to be an important pathway for olanzapine metabolism |
| *Metabolism during induction* |
| • Carbamazepine stimulates olanzapine metabolism by inducing both CYP1A2 and UGT1A4.47,48 Carbamazepine and other potent AED inducers are associated with a clinically relevant ↓ in olanzapine Cs, so that in the absence of TDM, it is recommended that the addition of carbamazepine for a patient taking olanzapine may require the olanzapine D to be multiplied by a factor of 2‑347 |
| • Omeprazole is a mild CYP1A2 inducer with effects similar to smoking26  |
| *TDM and C/D ratio* |
| • Therapeutic concentration range: 20-80 ng/ml11 |
| • Olanzapine C/D ratio: – Based on the literature,49‑51 a review of olanzapine C/D ratios52 found an average C/D ratio of:  · 1.5 ng/ml/mg/day in smokers and  · 2.5 ng/ml/mg/day in non-smokers – C/D ratios <0.5 ng/ml/mg/day indicate:  · The patient is not taking the medication or  · May be taking a powerful inducer (e.g., carbamazepine) – Other studies47,53,54 found C/D ratios ranging from 1.5 to 2.3 ng/ml/mg/day but did not account for smoking status |

AED: antiepileptic drug; C: concentration; C/D: concentration-to-dose; CYP: cytochrome P450; CYP1A2: CYP isoenzyme 1A2; CYP2D6: CYP isoenzyme 2D6; CYP3A4: CYP isoenzyme 3A4; D: dose; TDM: therapeutic drug monitoring; UGT1A4: uridine 5’-diphospho-glucuronosyltransferase 1A4.

**Supplementary Table S7 – Clozapine Pharmacokinetics**

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| *Metabolism* |
| • Metabolic pathways:55,56 – Main: to norclozapine through an N-demethylation pathway  – Other minor pathways include56:  · N-oxidation · Aromatic ring hydroxylation, and  · Glucuronidation |
| • Regarding CYP isoenzymes: – Using a 10-mg single oral dose in healthy volunteers, Bertilsson et al.:57 CYP1A2 explains 70% of clozapine metabolism – An in vitro study by Olensen et al.58 proposed that CYP metabolism depends on clozapine doses · At low concentrations, CYP1A2 is the most important pathway,  · but in higher concentrations, CYP2C19 is important, too · Other CYPs, such as CYP2C9, CYP2D6, and CYP3A4, had more modest roles |
| *TDM and C/D ratio* |
| • Therapeutic concentration range: 350-600 ng/ml11 |
| • The clozapine C/D ratio: – Is obtained by dividing the serum clozapine concentration (ng/ml) by the clozapine daily dosage (mg/day) – Provides clinicians with an idea of how a given D relates to the level of efficacy (clozapine is responsible for efficacy) – Typically ranges between 0.6 and 1.2 ng/ml/mg/day in the US:55  · US male smokers usually have a C ≥350 ng/ml with a D=600 mg/day: C/D ratio of 0.58 ng/ml/mg/day (350/600) · US female non-smokers usually have a C ≥350 ng/ml with a D=300 mg/day: C/D ratio of 1.17 ng/ml/mg/day (350/300)  |

C: concentration; C/D: concentration-to-dose; CYP: cytochrome P450; CYP1A2: CYP isoenzyme 1A2; CYP2D6: CYP isoenzyme 2D6; CYP2C9: CYP isoenzyme 2C9; CYP2C19: CYP isoenzyme 2C19; CYP3A4: CYP isoenzyme 3A4; D: dose; TDM: therapeutic drug monitoring; UGT1A4: uridine 5’-diphospho-glucuronosyltransferase 1A4.

**Supplementary Table S8 – Case 1. Diazepam responses**

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| *Planning sedation to visit the dentist*\* |
| • Because 30 mg/day of diazepam as an AED resulted in undetectable levels, a trial of the dose needed for sedation was planned with an additional dose of 80 mg of diazepam prior to going to the dentist:  – This was approved by the patient’s guardian, but was faced with reluctance from the nurse and the psychiatry resident involved in the treatment care. The psychiatry resident, born in China and probably a CYP2C19 PM, reported being sedated by 5 mg of diazepam and expressed concern that an extra dose of 80 mg was not safe  – A lower dose was tried. The addition of a 20-mg oral dose to the 30 mg/day of diazepam did not have any sedating effect – The next day, the addition of a 40-mg oral dose to the 30 mg/day of diazepam again had no sedating effect. – The day before the scheduled dentist appointment, 80 mg of oral diazepam was given at 3:00 PM (the patient had taken a 10-mg dose in the morning). The total dose of 90 mg led to mild dysarthria and a calm demeanor appearing effective for sedation |
| *Sedation with diazepam for initial dental visits* |
| • On the day of his appointment, the patient received 80 mg of diazepam 1 h prior to his appointment and he was able to sit in the dental chair and cooperate with dental work after more than 5 years without any dental work. The blood levels 2.5 h after the 80-mg dose was finally detectable were diazepam 1.1 ng/mL and nordiazepam 0.9 ng/mL with a total of 2.0 ng/mL |
| • The same dose of 170 mg in two days was successfully repeated again for the second and third dental visits, respectively one week and two weeks later. After each visit the diazepam was tapered off until the standard dose of 30 mg/day was reached  |
| *Progressively greater sedation with high doses of diazepam due to lack of induction*  |
| • Six months later and 9 months after phenytoin discontinuation, the same oral sedation protocol procedure was planned before going to the dentist (80 mg/day the prior day and 90 mg/day on the day of the visit). This time the outcome was different; the 80 mg given the day before the appointment was associated with intense sedation lasting for 85 min and a slow recovery. Then the next day, only 20 mg/day was given and the patient cooperated with the dentist. Oral diazepam was subsequently slowly tapered |
| • Another 6 months later and 15 months after phenytoin discontinuation, the patient was in mechanical restraints; he was very agitated for 5 h and, after repeated doses of diphenhydramine 50 mg, 2 doses of oral diazepam 30 mg were given, 1 h apart. 90 min after the first dose, he calmed down but appeared intoxicated with ataxia. This response to a total of 60 mg of diazepam appears to suggest that diazepam metabolism was becoming even slower than 6 months prior.  |
| *Normal diazepam response after 1.5 years from phenytoin discontinuation* |
| • Another 3 months later and 18 months after phenytoin discontinuation, he was in mechanical restraints and had been very agitated for 4 h; 100 mg of oral diphenhydramine and 2 mg of oral lorazepam were tried with no effect. Subsequently, 20 mg of oral diazepam calmed the patient down. At that time, a standing order of as-needed diazepam 20 mg to control agitation was written. In summary, it appears that after 1.5 years of phenytoin discontinuation, the patient was no longer an extremely fast metabolizer of diazepam, and appeared to have a normal response to 20 mg oral or IM of diazepam |

CYP2C19: CYP isoenzyme 2C19; IM: intramuscular.

\*When the patient’s behavior had become somewhat more stable, he was scheduled for an appointment with the hospital dentist, since he had not seen one for many years. Unfortunately, the patient ransacked the office, and prevented any dental care. Given his lack of response to trials of multiple medications and doses for agitation, greater attention to his sedative regimen was needed for a subsequent attempt. The list of past ineffective sedation medications included oral quetiapine (200 mg), IM haloperidol (5 mg), IM lorazepam (2 mg), oral chloral hydrate (500 mg), oral trazadone (50 mg), and oral diphenhydramine (50 mg).

**Supplementary Table S9 – Case 1. Diazepam and nordiazepam concentrations after 30 mg of oral diazepam and 30 mg of IM diazepam**

|  |  |
| --- | --- |
| Time after IM injection | Concentrations (ng/mL) |
| Diazepam | Nordiazepam  | Totala |
| Baselineb | <200 | <200 | <400 |
| 1 h | 500 | 200 | 700 |
| 1.5 hc | 400 | <200 | <600 |
| 3 h | 300 | 200 | 500 |
| 24 h | <200 | <200 | <400 |

AUC: area under the curve; IM: intramuscular.

aAUC of the total concentrations over 24 h was used to estimate diazepam clearance (clearance=AUD/dose). Using Winzip, the diazepam clearance was 77.6 ml/min. In the published literature we could find an estimation of diazepam clearance after IM diazepam. In 20 healthy young males given 11. 3 mg IM diazepam, the diazepam clearance after 172 h was 34.3 ml/min59. The diazepam clearance in our patient is probably underestimated due to the use of 24 instead of 72 h and because the commercial laboratory used to determine concentrations has a relatively high lower limit of detection, 200 ng/mL (or 0.2 mg/L).

bThe baseline and next-morning levels were undetectable.

cThe patient showed mild dysarthria that was at its maximum 1.5 h after dosing and disappeared after 3 h.

**Supplementary Table S10 – Case 1. Quetiapine TDM indicating fast metabolism**

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| *Very fast quetiapine metabolism during phenytoin treatment* |
| • When this patient was taking carbamazepine and phenytoin or phenytoin without carbamazepine: – D=700 mg/day (300 mg at noon and 400 mg at night); 50 mg lower than the maximum recommended D=750 mg/day60 – Trough Cs were undetectable (<10 ng/ml) – Trough C/D ratio <0.013 ng/mL/mg/day · This is at least 10 times lower than the expected trough C/D ratio of 0.13 ng/mL/mg/day on the 750-mg/day D29 |
| *Fast quetiapine metabolism after phenytoin discontinuation* |
| • Once phenytoin was discontinued:a  – D=700 mg/day  – Trough C=13 ng/ml  – Trough C/D ratio=0.017 ng/mL/mg/day (approximately 8 times lower than the normal trough C/D ratio of 0.1329) |
| • The patient received a 200-mg dose of oral as-needed quetiapine, in addition to his scheduled 700 mg/day:  – D=900 mg/day  – Peak C= 240 ng/ml one hour after the extra doseb – Peak C/D ratio=0.27 ng/mL/mg/day (3  times lower than the expected peak C/D ratio=1.0 ng/ml/mg/day on 750 mg/day in men30) |
| *Fast quetiapine metabolism continued months after phenytoin discontinuation* |
| • During the next 3 months on valproic acid as an AED and 3 to 5 months after phenytoin discontinuation: – D=700 mg/day of quetiapine  – C =18-38 ng/ml.  – Trough C/D ratios= 0.02-0.05 ng/mL/mg/day (2.6-6.5 times lower than the expected C/D ratio of 0.13 ng/mL/mg/day)29.  |

AED: antiepileptic drug; C: concentration; C/D: concentration-to-dose ratio; D: dose.

aThe disorganization and agitation decreased mildly so that the patient was able to sit for 10 min in a room with the treatment team. For the first time, a generalized resting tremor that included the patient's head and trunk was observed. According to the patient’s mother, the patient had always displayed a tremor when he was taking typical antipsychotics. The patient had been taking 80 mg of propranolol and 2 mg/day of benztropine was subsequently added.

bA peak C was obtained 1 h after 200 mg extra dose. The multicenter study30 provided mean peak Cs within 1-1.5 h of last dose. The patient’s peak C=240 ng/ml was close to 277 ng/ml seen in men with D=225 mg/day30). In summary, the patient had taken 900 mg/day, but his peak was close to what a normal person would have on 250 mg/day of quetiapine.

**Supplementary Table S11 – Case 1. Normal olanzapine and clozapine C/D ratios**

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| *Normal olanzapine C/D ratio*a |
| • For >12 months:  – D=2.5 mg/day  – Mean±SD of 16 C=4.4±2.6 ng/ml – Mean±SD of 16 trough C/D ratio=1.7±1.0 ng/mL/mg/day  |
| • For >9 months:  – D=5 mg/day  – Mean±SD of 6 Cs=7.2±1.9 ng/ml – Mean±SD of 6 C/D ratios=1.4±0.4 ng/mL/mg/day  |
| • For >6 months:  – D=10 mg/day  – Mean±SD of 3 Cs=11.7±0.6 ng/ml – Mean±SD of 3 C/D ratios=1.4±0.4 ng/mL/mg/day  |
| • For <1 month:  – D=12.5 mg/day  – 1 C=11 ng/ml – 1 C/D ratio=0.9 ng/mL/mg/day  |
| • The total olanzapine trialb lasted >2 years; its mean of 26 C/D ratios=1.6 ng/mL/mg/day is within normal range for a smoker52  |
| *Normal clozapine C/D ratio* |
| • The clozapine trial lasted 16 months:c – D=700 or 800 mg/day  – Mean±SD of 11 clozapine C/D ratios=0.80±0.11ng/mL/mg/day indicates a normal metabolism for men smokers – Mean±SD of 11 total clozapine C/D ratios=1.21±0.19 ng/mL/mg/day · The total clozapine C/D ratio is calculated by adding clozapine and norclozapine Cs |

C: concentration; C/D: concentration-to-dose ratio; D: dose.

aA D of 5 mg/day of olanzapine was subsequently added to his quetiapine. This occurred after more than 6 months of hospitalization. Two weeks after the addition of olanzapine, mild improvement was observed in his formal thought disturbance. The quetiapine was subsequently discontinued. A mild but significant improvement was observed in his formal thought disturbance, attention span and cognitive functions leading to transfer from the low-stimuli unit to the long-term unit. He continued to have a generalized tremor even though benztropine was increased to 4 mg/day.

bRelevant medications during this time were valproic acid 5200 mg/day8, benztropine 4 mg/day, and propranolol 80 mg/day most of the time (but ranging from 40-120 mg/day).

cRelevant medications during this time were valproic acid 5200 mg/day8 and propranolol 80 mg/day.

**Supplementary Table S12 – Case 1. Akathisia**

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| *Akathisia on quetiapine* |
| • On 700 mg/day of quetiapine there was no obvious akathisia, but the patient was also taking 80 mg/day of propranolola |
| • Akathisia on 900 mg/day of quetiapine but with a serum concentration equivalent <225 mg/day: One day an extra dose of quetiapine 200-mg dose was added and this was accompanied by  – An increase in the tremor, some abnormalities in gait, and – A noticeable increase in restlessness. The patient paced continuously and could not sit still. Due to his disorganized language, he could not answer questions regarding subjective restlessness. The senior author and the nurses agreed that the restlessness did not appear to be explained by his usual disorganized behavior. The patient appeared to suffer from a new problem, akathisia, in spite of the fact that he was taking propranolol. It was very remarkable that the akathisia became very evident the day the patient took 900 mg/day of quetiapine but the peak C corresponded approximately to less than 225 mg/day, according to the multicenter study50 |
| • Subsequent use of as-needed quetiapine was stopped and the akathisia resolved |
| • Benztropine ↑ to 3 mg/day resulted in slight improvement, but did not completely resolve his generalized Parkinsonian tremor |
| *Akathisia on olanzapine*b |
| • Three months after starting olanzapine 5 mg/day, the patient was so stable that he could be transferred from the low-stimulus unit to the treatment-refractory unit. Subsequently, his behavior fluctuated, resulting in some good days and some bad days. Overstimulation, the presence of unknown young females and the taunting behavior of some male peers appeared to trigger his decompensation. Olanzapine was decreased to 2.5 mg/day without any worsening of the psychotic symptoms. The tremor did not disappear even after increasing his benztropine to 6 mg/day |
| • Reappearance of akathisia on 2.5 mg/day of olanzapine when the propranolol dose was decreased: – Since blood pressure was normal but in the low range, the hospital internist decreased the propranolol from 80 to 60 mg/day and then to 30 mg/day. Ten days later, the patient became more violent and agitated and he appeared to suffer from akathisia again. Propranolol was increased slowly up to 120 mg/day and later on was reduced to the prior dosage of 60 mg/day |
| • Reappearance of akathisia on olanzapine when the dose was increased to 5 mg/day: – Three months later, a covering clinician increased the olanzapine dose from 2.5 mg/day to 5 mg/day in the presence of 60 mg/day propranolol and 4 mg/day benztropine. The patient appeared to develop a severe case of akathisia and had to be transferred to the low stimuli unit for 5 days, where he was treated with several as-needed doses of diphenhydramine and diazepam; 2 weeks later, the olanzapine dose was decreased to 2.5 mg/day again and the akathisia disappeared |
| *Lack of akathisia on clozapine* |
| • No akathisia appeared during a 14-month clozapine trial with doses up to 800 mg/day and therapeutic concentrations |

aIt appears that propranolol was started for hypertension several years before, but details of its onset could not be obtained.

bThe combination of 80 mg/day propranolol and 4 mg/day of benztropine permitted the patient to tolerate up to 12.5 mg/day of olanzapine. On the other hand, higher olanzapine doses did not provide better antipsychotic response than 2.5 mg/day of olanzapine.