Journal of Forensic and Legal Medicine 41 (2016) 65–71

Contents lists available at ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Original communication

The relevance of cytochrome P450 polymorphism in forensic medicine and akathisia-related violence and suicide

Selma J.M. Eikelenboom-Schieveld [a], Yolande Lucire [b], James C. Fogleman [c, *]

[a] Independent Forensic Services LLC, 32796 Edward Drive, Conifer, CO, 80433, USA
[b] Forensic Psychiatrist, Pharmacogeneticist, Suite 310, Level 3 203-223 New South Head Road, Point Piper, NSW, 2027, Australia
[c] Department of Biological Sciences, University of Denver, Denver, CO, 80208, USA

ARTICLE INFO

Article history:
Received 18 August 2015
Received in revised form
4 March 2016
Accepted 1 April 2016
Available online 9 April 2016

Keywords:
Akathisia
Antidepressants
Cytochrome P450 (CYP450)
Forensic pharmacogenetics
Homicide
Suicide

ABSTRACT

Adverse drug reactions and interactions are among the major causes of death in the United States. Antidepressants have been reported as causing suicide and homicide and share the class attribute of frequently producing akathisia, a state of severe restlessness associated with thoughts of death and violence. Medical examiners can now identify some pharmacogenetic interactions that cause drugs, deemed safe for most, to be lethal to others. Such deaths do not yet include medication-induced, akathisia-related suicides and homicides. An extrapyramidal side effect, akathisia is a manifestation of drug toxicity whose causes lie, *inter alia*, in drugs, doses, and co-prescribed medications that inhibit and compete for metabolizing enzymes, which may themselves be defective. In this paper, we report our investigation into adverse drug reactions/interactions in three persons who committed homicide, two also intending suicide, while on antidepressants prescribed for stressful life events. Their histories of medication use, adverse reactions and reasons for changes in medications are presented. DNA samples were screened for variants in the cytochrome P450 gene family; that produce drug metabolizing enzymes. All three cases exhibit genotype-based diminished metabolic capability that, in combination with their enzyme inhibiting/competing medications, decreased metabolism further and are the likely cause of these catastrophic events.

1. Introduction

Many drugs that cross the blood–brain barrier and a quarter of the medicines in general use are metabolized by the highly polymorphic cytochrome P450 system.[1] Blood levels of prescribed medicines can be pushed towards toxicity because of genetically determined metabolizing capacity, high doses, and interactions with co-prescribed CYP450 inhibitors and synergies. Genetics of the cytochrome P450 (CYP450) system are the otherwise invisible factor that can correlate with catastrophic behavioural disturbances. A forensic investigation combined with medication history, reports from observers, clinical records and a blood sample or a non-invasive swab from the living or dead can help elucidate the proximate, pharmacogenetic cause of death, suicide or violence. This determination can absolve persons charged with homicide (or abort the investigation), affect insurance pay-outs for suicide, provide an absolute defence of involuntary intoxication for the perpetrator of violence, and should protect a living person from getting more drugs with the same metabolic pathways as those that caused the problem.

1.1. Medication-induced akathisia violence, suicide and homicide

That antidepressants cause some people to commit suicide has been known since the advent of the tricyclic antidepressants in the late 1950s.[2] In the early 1980s, Shear, then Schulte described cases of violence, homicide and suicide associated with akathisia (from the Greek for "can't sit down"), in some people taking antipsychotic medications.[3–5] Since the late 1980s, "new generation" antidepressants have been prescribed for stressful life situations, but their adverse effects and clinical trial data and have not been fully disclosed.[6] Akathisia is a dangerous adverse effect of antidepressants, antipsychotics and some other drugs that cross the blood–brain barrier. Unlike delusion-driven homicide and depression-driven suicide, akathisia-related violence and suicidality can abate when medication is decreased, changed or slowly stopped. Suicidality and violence tend to get worse if the dose is not tapered slowly. In 1990,

* Corresponding author. Tel.: +1 (303) 871 3475.
E-mail addresses: s.eikelenboom@ifscolorado.com (S.J.M. Eikelenboom-Schieveld), lucire@ozemail.com.au (Y. Lucire), fogleman@du.edu (J.C. Fogleman).

http://dx.doi.org/10.1016/j.jflm.2016.04.003
1752-928X/

Teicher reported on cases of new and persistent suicidality on fluoxetine, the first of a series of serotonin-boosting antidepressants, marketed as "new generation antidepressants" SSRIs and SNRIs.[7] These new drugs carry a relative risk of suicide and akathisia violence several times that of older tri- or tetracyclic antidepressants, known as TCAs.[8] In 2003, Healy accessed company archives on court orders, inspected the clinical trials presented for their licensing, as well as epidemiological and follow-up studies, all containing evidence of SSRI-induced suicide.[9] This research contributed to the document: *United States Food and Drug Administration (FDA) Public Health Advisory: Worsening Depression and Suicidality in Patients Being Treated With Antidepressant* (March 22, 2004).[10] This text was mandated into product information for all antidepressants and further warned health care providers and care givers to monitor daily for anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania in persons treated for psychiatric and non-psychiatric conditions with antidepressants.[10] Fergusson et al. found suicide rates were double to treble those on placebo in 183 antidepressant trials.[11] After reviewing 373 antidepressant clinical trials on information provided by the drug companies, FDA conceded that they did cause suicide. In that review, the FDA relied on the drug companies' own information and persisted with the systemic error that, before Healy's review of early trials, they had obliterated the suicide effect. That is to say, FDA reviewers continued to code suicides that occurred in the run in-washout period and in withdrawal as "placebo suicides". In 2006, Stone et al. found that more suicides had occurred in some of these trials and had not been reported at all, and that half of them had been incorrectly coded as occurring on placebo.[12] In 2007, a Black Box suicide warning about increased suicidality (the highest form of alert) was extended to persons up to the age of 24.[13] Hostility is called "aggression" and "homicidal ideation" in some labels. "Emotional lability" is used when a subject is withdrawn from a trial because of suicidal ideation.

RxISK.org manages a website documenting over 6000 press reports of massacres, homicides, suicides, school and college shootings which date back to 1966, involving both old and new antidepressants and stimulants prescribed for attention deficit hyperactivity disorder. Some legal defences are described.[14] Recent finding show a significant association between SSRIs and violent crime for individuals 15–24 years old.[15] Acute neuroleptic- (and SRI-) induced akathisia (code 333.99) appeared in 1994 in the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM IV) along with its fluctuating associated features: restlessness, suicide attempts, aggression, symptoms of toxic psychosis and behavioural dyscontrol.[16] DSM-5 (2013) has acknowledged acute and tardive medication-induced akathisia, but the constellation of catastrophic associated features no longer appears, nor does withdrawal akathisia nor delayed post-withdrawal akathisia, all of which are often misinterpreted as the return of an illness.[17] Restlessness, aggression in thought and deed, suicidality, death wish, behavioural dyscontrol, confusion, delirium, cognitive impairment, changing variable moods and presentations can be manifestations of neurotoxicity.

Documents obtained in 1986 in a product liability suit against Eli Lilly revealed that the FDA had repeatedly warned that fluoxetine has a stimulant profile similar to amphetamines.[18] In 1998, from Pfizer's laboratories, Roger Lane confirmed that antidepressant manufacturers were aware that SSRI-induced akathisia and suicide cases were related, *inter alia*, to cytochrome P450 metabolizer status, as well as drug–drug interactions, slowing metabolism and prolonging half-life.[19] In 2003, Breggin reported patients taking SSRIs who deteriorated into mania, agitated depression and violence.[20] Before the FDA's concession, general causation of suicide and homicide by antidepressants had been established in a series of Daubert Hearings in American courts.[21] Expert evidence was compliant with Rule 702 of the Federal Rules of Evidence. Healy suggested it was automatism: "… a transient, non-recurrent mental malfunction caused by an external factor, whether physical or psychological, that the mind of an ordinary person would be unlikely to have withstood and that produces an incapacity to control his or her acts". Automatism refers to behaviour consequent on chemical lobotomy disrupting the connection between the frontal lobe and motor behaviour.

Moore et al. studied 1527 cases of violence reported for 31 drugs. They concluded, "Acts of violence towards others were a genuine and serious adverse drug event associated with a relatively small group of drugs".[22] Varenicline, a drug for smoking cessation, was followed by antidepressants, with fluoxetine and paroxetine having the highest ranking. Violence associated with venlafaxine and desvenlafaxine, a drug and its first metabolite, make that pair the most implicated in violence, which can manifest as suicide and/or on others, as homicide. This confirmed the finding of Barbui et al.[23] In the drugs companies' own trials presented for their licensing, "new generation" or "atypical" antipsychotics were found to carry double the risk of suicide on antidepressants.[24]

1.2. Drug metabolizing enzymes of the cytochrome P450 family

The cytochrome P450 family of enzymes metabolizes up to 80 per cent of xenobiotics and most drugs used in psychiatry.[25] Medicines interact with the cytochrome P450 system as substrates, inducers, inhibitors or any combination of the three.[26]

Metabolism is affected by extrinsic factors, doses, and co-prescribed medications as well as intrinsic factors: nutrition, age, iron status, liver health, gender and comorbidity.[27]

The population can be broadly divided by DNA testing into extensive, those being normal or "wild-type," intermediate, and poor metabolizers for five major genes involved in drug metabolism: CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. There is an additional category of ultra-rapid metabolizers (UM) for CYP1A2, for CYP2C19 due to the *17 allele, and for CYP2D6 due to gene duplication of alleles that code for extensive metabolizing. DNA testing can be done from blood or buccal swab. Changes in the sequence of amino acids in the genes result in variant alleles that produce drug-metabolizing enzymes (DMEs) that differ in metabolic ability.

Poor metabolizers (PMs) tend to have adverse drug reactions quickly, but intermediate metabolizers (IMs) in whom there is a slower and unrecognized build-up of a drug or its metabolites are also at risk. Ultra-rapid metabolizers (UMs) at CYP2D6 have been found to be at increased risk of death by suicide and intoxication, particularly if taking prodrugs, opioids, which need CYP2D6 to convert them into the effective analgesic, morphine.[28] With ultra-rapid metabolizers, blood levels of some antidepressants with short half-lives may fluctuate over a single day with intolerable effects and may never reach therapeutic levels. Fast metabolism poses a greater risk on withdrawal. Fast-changing levels of psychotropic substances, up or down, can cause behavioural changes, as the neurotransmitters in the brain react to reach some equilibrium. This phenomenon makes starting and stopping medication the most dangerous times for suicide and violence, but both can happen at any time, with stress, provocation, dose change, addition or subtraction of a medication. These toxic responses to antidepressants may occur early or later in treatment.

Forensic pharmacogenomics correlates genetic variations to response to drugs.[29] DNA testing can provide forensic examiners with a tool to investigate death caused by medication.[30] In 2000, forensic pharmacogenetics was first used to explain the death of a

nine-year-old child treated with a combination of methylphenidate, codeine and fluoxetine where the medical examiner reported fluoxetine toxicity. Finding that the child was defective in CYP2D6 capability aborted a homicide investigation of the parents by explaining the toxic level.[31] Lucire and Crotty reported ten akathisia homicides (and some attempts) committed by people taking antidepressants, not for mental illness, but for distress caused by their predicaments. These individuals also had diminishing mutations in the CYP450 family of metabolizing enzymes and all were taking medicines that further decreased metabolism by inhibition.[32]

DNA testing can be used to predict and avoid adverse drug reactions. The forensic perspective involves working backwards from the event, explaining the adverse drug reaction by reference to the subject's genotype and the effects of co-prescribed medications. In this paper, we have documented the clinical history, medication regime and genotypes of three persons who committed homicide. We propose that the three case studies are instances of antidepressant-induced, akathisia-related homicide where diminishing mutations in CYP450-encoding genes contributed to toxicity, along with high doses, substantial drug burden, drug–drug interactions, drug–gene and drug–gene–drug interactions, inhaler and alcohol use.

2. Materials and methods

The subjects were interviewed and medical files were studied to ascertain if mental illness was evident before medication was given and to establish reasons for prescribing or changing medications. Reports of events were evaluated and medication in use was correlated with what the subjects were thinking and feeling before and during the homicides.

Genetic testing was performed for CYP450 genes that metabolize the drugs in use: CYP2D6, CYP2C9, CYP2C19 and, when available, for CYP1A2, CYP3A4 and CYP2B6. DNA sampling was done by buccal swap. DNA isolation was performed by Independent Forensic Services in Hulshorst, The Netherlands, using the QIAamp Investigator Kit (Qiagen). Cytochrome P450 genotyping was performed by the Erasmus University Medical Center, Rotterdam, The Netherlands. For CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/A5 by using the TaqMan® Drug Metabolism Genotyping Assays (ThermoFisher Scientific) and PCR-RFLP. Genotyping of CYP2D6 was performed using the AmpliChip Test (Roche Molecular Diagnostics), which is specific for CYP2D6 variants.

Information on CYP450 alleles, drug–gene, and drug–drug interactions was obtained from online databases: The Human Cytochrome P450 (CYP) Allele Nomenclature Database (www.cypalleles.ki.se), maintained by the Karolinska Institutet, Stockholm, Sweden[33]; SuperCYP (bioinformatics.charite.de/supercyp), maintained by the Institute of Molecular Biology and Bioinformatics, the Charité, Berlin, Germany[34]; and PharmGKB (www.pharmgkb.org), managed by Stanford University, Stanford, CA, USA.[35]

3. Subject 1, USA

A 39-year-old woman, with no prior history of mental illness, suicidality or violence had a difficult marriage and was prescribed zolpidem 10 mg/night for insomnia and alprazolam for fear of flying. A year later, she had divorced, moved to a new house, a parent had died, and she felt overwhelmed. Sertraline, 50 mg/day, was superimposed on long-term zolpidem use. Her mental state deteriorated. She said she had no emotions and felt like a “zombie”. She was switched to venlafaxine 150 mg/day. Throughout her treatment, she had been restless and had slept only with zolpidem, waking after few hours in an agitated state. At some point, she began believing that killing her husband and herself was the right thing to do for her children. She stopped venlafaxine abruptly and, on the following day, she ambushed her husband with a baseball bat, then stabbed him many times. Intent on committing suicide, she overdosed on zolpidem, alprazolam and alcohol, but survived and was charged with murder. The metabolic pathways of the drugs in use are presented in Table 1. Her P450 genotypes for the relevant enzymes are presented in Table 2.

3.1. Discussion

Her genotypes, *CYP2D6*5/*41, CYP2C9*1/*1 CYP2C19*2/*17* and *CYP3A4*1/*22*, characterize her as a very poor metabolizer with diminished capacity involving four out of eight alleles tested across four genes (Table 2). The effect of long-term zolpidem would be to further inhibit CYP1A2, CYP2D6, and CYP2C9, which would likely have increased her blood levels of zolpidem, a drug associated with homicidal behaviour, both on its own and in conjunction with SSRIs.[36] The addition of sertraline to zolpidem, *i.e.*, adding a substrate to an inhibitor (pattern 2 described by Armstrong et al.), would likely have provoked an adverse drug reaction, psychic numbing and worsening depression.[37] She would have had very little metabolizing capacity left for zolpidem and venlafaxine. Both have similar, synergistic neurotoxic effects, and this may be as significant clinically as the interaction. Venlafaxine is primarily metabolized by CYP2D6 and CYP3A4, and its psychoactive metabolite, desvenlafaxine, is a substrate of CYP3A4. Some databases suggest that CYP2C19 or CYP2D6 may play a part in metabolizing desvenlafaxine, but this information remains uncertain.

In this person, the activity of CYP2D6, a high-affinity but low-capacity enzyme, would have been greatly reduced, compromised by a diminished activity allele, *41, and a gene deletion, *5. CYP3A4 was also genetically compromised. Its enzymatic activity would have been further diminished due to inhibition by long-term sertraline use and substrate competition (between desvenlafaxine, sertraline, and zolpidem). The reduction of metabolic capacity for venlafaxine would be expected to prolong its half-life, likely taking the level over the therapeutic window and into a level that was toxic for that person (with possible input from variants in the genetics of transporters and receptors for which testing is not yet commercially available). While CYP2C9 and CYP2C19 are said to play a minor role in the metabolism of sertraline and zolpidem, all enzymes can be promiscuous and facilitate metabolism, albeit less effectively, under these conditions.[38] Substrate competition for enzymes by all three drugs made further demands on limited enzymatic capacity: CYP2C9 being inhibited by both zolpidem and sertraline and CYP2C19 being inhibited by sertraline. Increasing toxicity could have resulted in delirium, making her simultaneously euphoric and homicidal. Possibly experiencing drug toxicity, she stopped venlafaxine without tapering, and the rapid fall in blood level coincided with her behaviour. A similar case has been described, involving imaginary altruism that caused a loving father in a paroxetine-induced state of euphoria combined with homicidal ideation to kill his child.[32]

Table 1
Drugs and metabolic pathways used by Subject 1 (data from SuperCYP).

	CYP1A2	CYP2B6	CYP2D6	CYP2C9	CYP2C19	CYP3A4
Zolpidem	Sub Inh		Inh Sub	Sub Inh	Sub	Sub
Sertraline	Sub	Inh Sub	Sub Inh	Sub Inh	Sub Inh	Sub Inh
Venlafaxine		Inh	Sub Inh	Sub	Sub	Sub Inh
Desvenlafaxine						Sub

Sub: Substrate; Inh: Inhibitor.

Table 2
Genotypes and expected phenotypes for Subject 1.

Genotype	*In vitro* activity	Gene–drug, drug–gene and drug–drug interactions	Phenotype
*CYP2D6*5/*41*	*5 gene deletion *41 diminished	venlafaxine is both a substrate and inhibitor of CYP2D6, which is genetically compromised	further diminished activity, possibly no activity
*CYP3A4*1/*22*	*1 normal *22 diminished	desvenlafaxine, sertraline, and zolpidem are substrates of CYP3A4 and compete for the enzyme, which is inhibited by both sertraline and venlafaxine	further diminished activity by inhibition and competition
*CYP2C9*1/*1*	normal	zolpidem, sertraline, and venlafaxine are substrates of CYP2C9 and compete for the enzyme, which is inhibited by venlafaxine	further diminished activity by inhibition and competition
*CYP2C19*2/*17*	*2 inactive *17 ultrarapid	zolpidem, sertraline, and venlafaxine are substrates of CYP2C19 and compete for the enzyme, which is inhibited by sertraline	further diminished activity by inhibition and competition

Based on the pharmacogenetic analysis, we hypothesize that poor drug metabolism and drug–gene–drug interactions caused a CYP450-based adverse drug reaction resulting in a medication-induced homicide. Inhibition of its own metabolism by zolpidem and, by the same means, the inhibition of the metabolism of antidepressants, may explain why it its product information advises that zolpidem should not be used for more than three weeks and why it should not be combined with an SSRI. Adverse effects of venlafaxine include abnormal thinking, abnormal/changed behaviour, aggressive reaction, akathisia, amnesia, apathy, confusion, delusions, dementia, depersonalization, emotional lability, euphoria, hallucinations, hostility, homicidal ideation, illusion, impulse control difficulties, manic reaction, paranoid reaction, psychosis, depression and illusion, suicidal ideation and attempt, psychotic and worsening depression.[39] Adverse effects listed for zolpidem are synergistic and include confusion, euphoria, insomnia, agitation, anxiety, decreased cognition, difficulty concentrating, dysarthria, emotional lability, hallucination, illusion, nervousness, speech disorder, abnormal thinking, aggressive reaction, delusion, dementia, depersonalization, dysphasia, feeing strange, hysteria, intoxicated feeling, manic reaction, personality disorder and suicide attempts.[40]

Subject 1 took a plea bargain for second-degree murder and received a lengthy prison sentence. The pharmacogenetic evidence was brought up during the sentence appeal. A drug-screen for venlafaxine had been performed, but five days after her last dose. The coroner's laboratory, apparently unaware that drugs are not detectable after five half-lives, reported that the absence of venlafaxine in her blood meant that she had never used it.

4. Subject 2, Holland

A 33-year old woman with marriage problems became depressed and preoccupied with death, but had no delusions or hallucinations. She was hospitalized and treated for anxiety and depression with sertraline and temazepam, and then quetiapine was added for persistent insomnia. On this combination, she experienced severe fatigue, experienced weird thoughts that she recognized as such, remained gloomy, and failed to recover. She improved when her husband was hospitalized with a psychiatric breakdown but deteriorated again when he came home. She reported mood swings and panic attacks. Her doctor thought she was delusional. A year later, she was hospitalized and switched to venlafaxine 150 mg/day, which is 2–4 times the recommended starting dose. A couple of months later, the note, “this patient does not belong in psychiatric care,” was recorded, and she was discharged. Venlafaxine was reduced to 75 mg/day, and temazepam and quetiapine were ceased. After nine months, she stopped venlafaxine without tapering but, two weeks later, she resumed her prescribed dosage. Her behaviour was described as “erratic” and “chaotic”. Without warning, she suffocated her two-year-old son with a pillow, hanged him using the cord of her bathrobe, put him in a box, woke her 7-year-old-daughter and told her that they all, including herself, had to die. She drove a car, along with her daughter, into a canal. Her daughter escaped. Charged with murder and attempted murder, she had only patchy recall of these events. Drugs and enzymes for this subject are given in Table 3. A year later, the defence team requested genetic testing for CYP450 (Table 4).

4.1. Discussion

Her genotypes, *CYP2D6*2/*2* and *CYP2C19*1/*1* were normal, but *CYP2C9*1/*3* and *CYP3A4*3/*22* are those of an intermediate metabolizer for both CYP2C9 and CYP3A4 (Table 4). Her toxic problems started with the first prescription of serotonergic antidepressants, sertraline, temazepam, and then quetiapine (a drug marketed as an antidepressant/antimanic/antipsychotic and also as a sleeping pill while subject to the FDA antidepressant advisories) for situational depression. She failed to recover, and her doctor thought she was delusional, but the criterion of a delusion, a fixed belief impervious to reason, was not met. Again, all three drugs interacted, and their listed side effects include abnormal thinking, aggression, akathisia, amnesia, confusion, delirium, delusions, depression, emotional lability, euphoria, hallucinations, manic reaction, paranoid reaction, paroniria, psychosis, suicidal ideation, attempts and suicide. Over time, sertraline most likely inhibited and depleted her diminished CYP2C9, and sertraline and quetiapine inhibited and depleted CYP2D6, leaving her with little or no enzyme capacity to metabolize her medicines. She developed Adverse Effects of Medication NOS (DSM IV TR and DSM-5 995.2) necessitating hospitalization and medication change. Venlafaxine was introduced, adding a drug that is both substrate and inhibitor of CYP2D6.

Further inhibition of CYP2D6 by venlafaxine over time would be expected to elevate its blood levels, resulting in her decision to cease taking it. Sudden withdrawal caused problems, and this may be the reason she restarted it. CYP2D6 is a low-capacity enzyme, which can be overwhelmed, converting even an extensive metabolizer into a poor metabolizer. CYP3A4, on the other hand, is a high-capacity, low-affinity enzyme, notoriously promiscuous and unpredictable, and it picks up metabolism when other enzymes are not available.[41] As with Subject 1, venlafaxine, by inhibiting

Table 3
Drugs and metabolic pathways used by Subject 2 (data from SuperCYP).

Drug	CYP1A2	CYP2B6	CYP2D6	CYP2C9	CYP2C19	CYP3A4
Sertraline	Sub	Inh Sub	Sub Inh	Sub Inh	Sub Inh	Sub Inh
Quetiapine			Sub Inh		Sub	Sub
Temazepam		Sub		Sub	Sub	Sub
Venlafaxine		Inh	Sub Inh	Sub	Sub	Sub Inh
Desvenlafaxine						Sub

Sub: Substrate; Inh: Inhibitor.

Table 4
Genotypes and expected phenotypes for Subject 2.

Genotype	*In vitro* activity	Gene–drug, drug–gene and drug–drug interactions	Phenotype
*CYP2D6*2/*2*	*2 extensive	venlafaxine is a substrate of CYP2D6, which it also inhibits	diminished activity by inhibition and competition
*CYP2C9*1/*3*	*1 active *3 inactive	venlafaxine is a substrate of CYP2C9	diminished activity
*CYP2C19*1/*1*	normal	venlafaxine is a substrate of CYP2C19	normal activity for venlafaxine
*CYP3A4*3/*22*	*3 diminished *22 diminished	desvenlafaxine and venlafaxine are substrates for CYP3A4 which is inhibited by venlafaxine	further diminished activity by inhibition and competition, possibly no activity

CYP2D6, inhibited its own metabolism. CYP3A4 was genetically compromised as well as inhibited. Her metabolic capability was reduced. A toxicology screen performed on the day of the homicide showed a toxic range in the blood with a total 2.29 mg/L, combining venlafaxine: 0.59 mg/L and desvenlafaxine: 1.7 mg/L. The agreed therapeutic range at that laboratory for the two drugs combined is between 0.2 and 0.75 mg/L, with toxic effects starting at 1.0 mg/L.

The phenomenon of dose-dependent inhibition of CYP2D6 increasing with blood levels over time applies to other antidepressants. With daily doses, blood levels may rise. By introducing inhibition of enzymes as well as competition for them, polypharmacy increases the risk of catastrophic side effects.[42] After Andrea Yates drowned her six children in a bathtub while taking venlafaxine, mirtazapine and several other substances, Wyeth, while denying causation, then added homicidal ideation to the list of adverse effects.[43]

Substance-induced homicidal ideation is biological and involuntary as are somatic adverse reactions. When homicidal thinking is associated with mood elevation, euphoria, it becomes homicidal mania. Involuntary, out-of-character, and uncontrollable violent thoughts should not be taken as evidence of planning. Akathisia is sometimes masked by akinesia, fatigue that "ropes you to the bed". Patients stop taking medicines if they experience their effects as intolerable, and unknowingly risk withdrawal effects, which are often more severe. The post-withdrawal period is as dangerous as the initial period for suicide and homicide.[44] The combination of medication, fluctuating restlessness, suicidality, aggression and toxic hallucinosis are pathognomonic of akathisia. We cannot find any other diagnosis in any medical taxonomy that combines suicidal and aggressive thoughts and behaviours with medication, nor any other that recedes when the culprit medication has been stopped slowly.

5. Subject 3, Holland

A 42-year-old man, with no history of mental illness, suicidality or violence, discovered that his wife was unfaithful, but they stayed together. He was prescribed paroxetine 20 mg/day for his distress. He took it sporadically, when he felt that he needed something for his nerves. Some months later, after drinking alcohol and taking 20 mg of paroxetine, he tried to strangle his wife with the sash of her bathrobe. She hit him, and he stopped the attack, but he did not remember what he had done. His doctor failed to recognize this as an akathisia event, and added oxazepam 30 mg/day to be taken in divided doses. Subject 3 gave this medication to a person who also had marital problems, saying he would take an "extra paroxetine tablet" if he felt depressed. Two weeks later, he drank a dozen glasses of beer in a bar, took 40 mg of paroxetine and used his asthma inhaler containing budesonide/formoterol. How long he had used that inhaler and how many doses he used is not known. According to witnesses, he was neither drunk nor aggressive when he left. On the way home, he saw the car of his now-estranged wife in front of the house of his rival, and he called her on his cell phone. When she refused to talk to him, according to his statement, his "lights went out". He went home, picked up an antique revolver and a hammer and returned to the house of his rival. He reported that he could see them inside on the couch. He then smashed the window with the hammer and climbed through it, cutting himself and leaving blood. He said that he "felt nothing" and was "like a robot". He shot his wife and rival, who both survived. He then drove to the house of the rival's wife, whom he blamed for coming between himself and his own wife. He forced entry into her house and shot her fatally. He reported feeling both hot and cold and shaking violently. He drove for some hours before turning himself in to the authorities. No toxicology screen was performed. He was charged with murder and two attempted murders, convicted and sentenced to 24 years in jail.

On appeal, his lawyer raised the defence that paroxetine had caused this behaviour. Toxicology conducted on dried bloodstains detected paroxetine above the threshold of 10 ng/mL (blood), but the exact level could not be determined. The metabolic pathways of the drugs in use are presented in Table 5. During the appeal, DNA testing for P450 genotypes was performed (Table 6).

5.1. Discussion

His genotypes, *CYP2D6*2/*9, CYP2B6*1/*6, CYP2C9*1/*1 CYP2C19*6/*17* and *CYP3A4*1/*1*, characterize him as an intermediate metabolizer (IM) with diminished capacity involving three out of ten alleles tested across five genes. Paroxetine is a potent inhibitor of CYP2D6, and over time, converts 80 per cent of extensive metabolizers into poor metabolizers.[45] CYP2D6 was genetically compromised, by the diminished activity allele, *9. Paroxetine also inhibits CYP1A2, CYP2C19 and CYP3A4. Possible competition between paroxetine and formoterol in his inhaler may slow the rate at which either is metabolized. According to Jornil et al., CYP2D6 (high affinity) and CYP3A4 (low affinity) are most likely the major contributors to paroxetine metabolism. CYP1A2 could an important factor, whereas the importance of CYP2C19 is probably limited.[46] Alcohol inhibits CYP2B6, CYP2C9, CYP2C19, and, given the alcohol content of 12 beers, also CYP3A4. Alcohol is a substrate for CYP1A2. The competition between paroxetine, alcohol and budesonide for CYP2D6 and CYP3A4 may have increased toxicity. He was extensively evaluated and no evidence of personality disorder, psychiatric illness, aggression or impulsivity was found.[47] Alcohol, on its own, had not caused violent behaviour in this individual before. In

Table 5
Drugs and metabolic pathways used by Subject 3 (data from SuperCYP).

	CYP1A2	CYP2B6	CYP2D6	CYP2C9	CYP2C19	CYP3A4
Alcohol	Sub	Inh		Inh	Inh	Ind Sub Inh[a]
Paroxetine	Inh	Inh	Inh Sub	Inh	Inh	Inh
Budesonide						Sub
Formoterol			Sub	Sub	Sub	

Sub: Substrate; Inh: Inhibitor; Ind: Inducer.
[a] Alcohol induces CYP3A4 at low levels and inhibits it at high levels.

Table 6
Genotypes and expected phenotypes for Subject 3.

Genotype	*In vitro* activity	Gene–drug, drug–gene and drug–drug interactions	Phenotype
*CYP2D6*2/*9*	*2 active *9 diminished	paroxetine is a substrate of CYP2D6 and inhibits it strongly; formoterol competes for CYP2D6	further diminished activity by inhibition and competition
*CYP2B6*1/*6*	*1 active *6 diminished	paroxetine and alcohol both inhibit CYP2B6	further diminished activity by inhibition
*CYP2C9*1/*1*	normal	paroxetine and alcohol inhibit CYP2C9; formoterol is a substrate	further diminished activity by inhibition
*CYP2C19*6/*17*	*6 no activity *17 ultrarapid	paroxetine and alcohol inhibit CYP2C9; formoterol is a substrate	further diminished activity by inhibition
*CYP3A4*1/*1*	normal	paroxetine inhibits 3A4. Low levels of alcohol induce while high levels inhibit CYP3A4. Budesonide and alcohol are substrates for CYP3A4	further diminished activity by inhibition and competition

2014, Menkes and Herxheimer reported on a syndrome of pathological intoxication by alcohol in patients being treated with SSRI antidepressants.[48] The hot and cold sensations and restless driving all suggest acute serotonin toxicity and associated akathisia.

6. Overall discussion

Three persons committed homicide, two of which intended to commit suicide. None had been aggressive or mentally ill before getting medication. None had known that they needed to take medication regularly or how to stop taking it safely. None improved on medication, and no prescriber recognized their complaints as adverse drug reactions or was aware of impending danger. Interviews elicited accounts of restlessness, akathisia, confusion, delirium, euphoria, extreme anxiety, obsessive preoccupation with aggression, and incomplete recall of events. Weird impulses to kill were acted on without warning. On recovery, all recognized their actions to be out of character, and their beliefs and behaviours horrified them.

All were prescribed interacting medications, and one combined these with alcohol. The drug–drug interactions further decreased their metabolizing capacity, increasing risk for adverse drug reactions by prolonging half-life and raising levels. This paper elucidates the necessary elements of an inquiry after a suicide attempt, a homicide, or a violent crime. DNA testing can provide evidence for legal proceedings. Cytochrome P450 genotyping can assist in the interpretation of toxicology.[49] The promise of Personalized Medicine is that determination of a person's metabolizing capacity before drug treatment or after an adverse event will avoid catastrophic events in the future. Pharmacogenetics paves the way for personalized justice[50–52]

7. Summary

A forensic investigation of the serious problem of akathisia-related violence requires several elements: first, blood needs to be taken for a toxicology screen as soon as possible after the event. Blood left at the crime scene may confirm medication use and sometimes drug levels, but blood taken late does not exclude toxicity at the relevant time. Second, pharmacogenetic testing should be performed for (at least) CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. The investigator needs to access reliable information: the metabolic pathways of drugs in use, their interactions with genes and with each other. No one stores this knowledge about 2000 drugs, so it is accessed through charts and medical informatics programs. Familiarity with symptoms, signs and behaviours associated with neuroleptic toxicity is needed to focus the history of experience and behaviour, which can be taken from a perpetrator, a family member, or an observer, and can be assisted by clinical records. Establishing the behavioural aspects of akathisia, the fluctuating restlessness, the behavioural toxicity prior to the event supports that diagnosis. This restlessness is associated with thoughts of death, dying, and killing, and such thoughts can be acted on without warning. Dysphoria, emotional distress that cannot easily be articulated, ranges in intensity from mild discomfort to one of the most painful mental states known to psychiatry, often described as torture – so bad that death is seen as a welcome relief. An out-of-character unmotivated homicide or suicide by a person taking medication might be chemically induced and involuntary. The capacity to use frontal lobe functions and control behaviour can be impaired by brain toxicity. A “chemical lobotomy” could be the outcome.

CYP450 status is an important factor that differentiates those who can tolerate a drug or combination of drugs from those who might not. Testing for cytochrome P450 identifies those at risk for such adverse drug reactions. As forensic medical and toxicology professionals become aware of the biological causes of these catastrophic side effects, they may bring justice to both perpetrators and to victims of akathisia-related violence. The medicalization of common human distress has resulted in a very large population getting medication that may do more harm than good by causing suicides, homicides and the mental states that lead up to them.[53]

Conflict of interest
No conflict of interest to declare.

Funding
No funding was provided.

Ethical approval
This research was approved by the University of Denver's Institutional Review Board (IRB), and is in compliance with all regulations regarding human subjects research.

Acknowledgements

DNA testing for CYP450 genotypes was performed by Prof. R.H.N. van Schaik, Department of Clinical Chemistry, Erasmus University Medical Center in Rotterdam, The Netherlands.

References

1. Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *Am Fam Physician* 2007;**73**(3):391–6.
2. Mayer-Gross W, Slater E, Roth M. *Clinical psychiatry*. Cassell; 1954.
3. Shear KM, Francis A, Weiden P. Suicide associated with akathisia and depot fluphenazine treatment. *J Clin Pharmacol* 1983;**3**(4):235–6.
4. Schulte JL. Homicide and suicide associated with akathisia and haloperidol. *Am J Foren Psychiatry* 1985;**6**:3–7.
5. Cem AE, Schultz SK, Andreasen NC. The relationship of akathisia with suicidality and depersonalization among patients with schizophrenia. *J Neuropsychiatry Clin Neurosci* 2001;**13**(3):336–41.

6. Breggin PR. How GlaxoSmithKline suppressed data on paxil-induced akathisia: implications for suicidality and violence. *Ethical Hum Psychol Psych* 2006;**8**(2):91–100.
7. Teicher MH, Glod CA, Cole JO. Antidepressant drugs and the emergence of suicidal tendencies. *Drug Saf* 1993;**8**(3):186–212.
8. Maris RWM. *Suicide and neuropsychiatric adverse effects of SSRI medications: methodological issues*. 2002. Philadelphia, Pennsylvania, http://psychrights.org/Research/Legal/Evidence/MarisonSSRIsUnderDaubert.htm [accessed 06.05.15].
9. Healy D. Lines of evidence on the risks of suicide with selective serotonin reuptake inhibitors. *Psychother Psychosom* 2003;**72**(2):71–9.
10. United States Food and Drug Administration. *Class suicidality labeling language for antidepressants*. 2007. http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/20031s045,20936s020lbl.pdf [accessed 29.04.15].
11. Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005;**330**(7488):396–9.
12. Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ* 2009;**339**:b2880.
13. United States Food and Drug Administration. *Revisions to product labeling*. 2007. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM173233.pdf.
14. RxISK.org. SSRI Stories Antidepressant nightmares. SSRI Stories n.d. http://ssristories.org/[accessed 06.05.15].
15. Molero Y, Lichtenstein P, Zetterqvist J, Gumpert CH, Fazel S. Selective serotonin reuptake inhibitors and violent crime: a cohort study. *PloS Med* 2015;**12**(9):e1001875.
16. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. Text Revision. 4th ed. Washington, DC: American Psychiatric Association; 2000.
17. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. DSM-5. 5th ed. Washington, D.C: American Psychiatric Publishing; 2013.
18. Healy D. *Let them eat prozac*. James Lorimer & Company; 2003. p. 464.
19. Lane RM. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. *J Psychopharmacol* 1998;**12**(2):192–214.
20. Breggin PR. Suicidality, violence and mania caused by selective serotonin reuptake inhibitors (SSRIs): a review and analysis. *Int J Risk Saf Med* 2004;**16**:31–49.
21. Healy D. *Let them eat prozac*. Website – Index; 2003. http://www.healyprozac.com/ [accessed 20.03.2015].
22. Moore TJ, Glenmullen J, Furberg CD. Prescription drugs associated with reports of violence towards others. *PLoS One* 2010;**5**(12):e15337.
23. Barbui C. Antidepressants and the risk of suicidal behaviors: comment. *JAMA* 2004;**292**(23):2833.
24. Healy D. Shaping the intimate: influences on the experience of everyday nerves. *Soc Stud Sci* 2004;**34**(2):219–45.
25. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J* 2005;**5**(1):6–13.
26. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther* 2013;**138**(1):103–41.
27. Preskorn SH, Flockhart D. 2006 guide to psychiatric drug interactions. *Prim Psychiatry* 2006;**13**(4):35–64.
28. Zackrisson A-L. *Pharmacogenetics from a forensic perspective: CYP2D6 and CYP2C19 genotype distributions in autopsy cases*. 2009. http://www.diva-portal.org/smash/record.jsf?pid=diva2:213011 [accessed 26.03.15].
29. Riccardi LN, Bini C, Ceccardi S, Trane R, Luiselli D, Pelotti S. CYP2D6 polymorphism studies: how forensic genetics helps clinical medicine. *Forensic Sci Int Genet Suppl Ser* 2009;**2**(1):485–6.
30. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;**279**(15):1200–5.
31. Sallee FR, DeVane CL, Ferrell RE. Fluoxetine-related death in a child with cytochrome P-450 2D6 genetic deficiency. *J Child Adolesc Psychopharmacol* 2000;**10**(1):27–34.
32. Lucire Y, Crotty C. Antidepressant-induced akathisia-related homicides associated with diminishing mutations in metabolizing genes of the CYP450 family. *Pharmacogenomics Pers Med* 2011;**4**:65–81.
33. Sim SC, Ingelman-Sundberg M. The Human Cytochrome P450 (CYP) Allele Nomenclature website: a peer-reviewed database of CYP variants and their associated effects. *Hum Genomics* 2010;**4**(4):278–81.
34. Preissner S, Kroll K, Dunkel M, Senger C, Goldsobel G, Kuzman D, et al. SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. *Nucleic Acids Res* 2010;**38**:D237–43.
35. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther* 2012;**92**(4):414–7.
36. Paradis CM, Siegel LA, Kleinman SB. Two cases of zolpidem-associated homicide. *Prim Care Companion CNS Disord* 2012;**14**(4). PCC.12br01363.
37. Armstrong SC, Cozza KL, Sandson NB. Six patterns of drug–drug interactions. *Psychosomatics* 2003;**44**(3):255–8.
38. Hopkins AL, Mason JS, Overington JP. Can we rationally design promiscuous drugs? *Curr Opin Struct Biol* 2006;**16**(1):127–36.
39. Wyeth Pharmaceuticals. *Philadelphia, PA 19101. Effexor XR® (venlafaxine hydrochloride) extended release capsules (label)*. 2008.
40. Highlights of Prescribing Information (Ambien) Revised 2/2008. http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019908s027lbl.pdf [accessed 11.05.2015].
41. Flockhart DA, Rae JM. Cytochrome P450 3A pharmacogenetics: the road that needs traveled. *Pharmacogenomics J* 2003;**3**(1):3–5.
42. Popli A, Gupta S. Polypharmacy akathisia and associated suicide attempts. *Depression* 1993;**1**(1):53–5.
43. Spinelli MG. Infanticide. *JAMA* 2004;**292**(17):2157–8.
44. Healy D. The antidepressant tale: figures signifying nothing? *Adv Psychiatr Treat* 2006;**12**(5):320–7.
45. Žourková A, Hadašová E. Paroxetine-induced conversion of cytochrome P450 2D6 phenotype and occurrence of adverse effects. *Gen Physiol Biophys* 2003;**22**(1):103–13.
46. Jornil J, Jensen KG, Larsen F, Linnet K. Identification of cytochrome P450 isoforms involved in the metabolism of paroxetine and estimation of their importance for human paroxetine metabolism using a population-based simulator. *Drug Metab Dispos* 2010;**38**(3):376–85.
47. Giancola PR. The moderating effects of dispositional empathy on alcohol-related aggression in men and women. *J Abnorm Psychol* 2003;**112**(2):275–81.
48. Menkes DB, Herxheimer A. Interaction between antidepressants and alcohol: signal amplification by multiple case reports. *Internat J Risk Saf Med* 2014;**26**:163–70.
49. Druid H, Holmgren P, Carlsson B, Ahlner J. Cytochrome P450 2D6 (CYP2D6) genotyping on postmortem blood as a supplementary tool for interpretation of forensic toxicological results. *Forensic Sci Int* 1999;**99**(1):25–34.
50. Kupiec TC, Raj V, Vu N. Pharmacogenomics for the forensic toxicologist. *J Anal Toxicol* 2006;**30**(2):65–72.
51. Sander T, Noll L, Wong SH, Peterson BL, North PE. Pharmacogenetics testing for forensic pathology paves the way for "Personalized Justice." *FASEB J* 2011;**25**(12):793 (meeting abstrs).
52. Wong SH, Happy C, Blinka D, Gock S, Jentzen JM, Donald Hon J, et al. From personalized medicine to personalized justice: the promises of translational pharmacogenomics in the justice system. *Pharmacogenomics* 2010;**11**(6):731–7.
53. Insel TR. Disruptive insights in psychiatry: transforming a clinical discipline. *J Clin Invest* 2009;**119**(4):700–5.