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

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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

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medication is decreased, changed or slowly stopped. Suicidality and violence tend to get worse if the dose is not tapered slowly. In 1990, 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