REVIEW ARTICLE

Treatment Emergent Violence To Self And Others; A Literature Review of Neuropsychiatric Adverse Reactions For Antidepressant And Neuroleptic Psychiatric Drugs And General Medications

Catherine Clarke SRN, SCM, MSSCH, MBChA; Jan Evans, MCSP Grad Dip Phys; Kelly Brogan, MD

ABSTRACT

Objective • This paper reviews the literature linking physical violence, directed towards self or others, to serotonergic and dopaminergic psychiatric drugs and general medications.

Design/methodology/approach • Data about side effects, pharmacogenetics and homeostasis are obtained from articles, electronic Medicines Compendium, DSM-IV-TR, British National Formulary (BNF) and academic books. Statistics have been obtained from articles, The National Confidential Inquiry into Suicide and Homicide by People with Mental Illness, Centre for Mental Health and Risk, Manchester, Mental Health Equalities, National Mental Health Development Unit and the NHS Health and Social Care Information Centre. Classification for neurotoxic conditions and mental illness are obtained from the DSM-IV-TR, DSM-V and ICD-10.

Findings • Psychiatric drugs and some general medications have effects that are not always the ones intended. Reactions to different drugs and drug-drug combinations are governed by individual metabolising rates. Phase 1 metabolism takes place via the cytochrome P450 enzymes with 57 human genes identified that are genetically variable i.e. polymorphic. The population are coded as poor, extensive (known as normal), intermediate or ultra rapid metabolisers.

Variations in the serotonin transporter gene (5-HTTLPR) and serotonin receptors (5-HT) influence the outcome of serotonergic medications. It is established genetic polymorphisms in the CYP450 and serotoninergic metabolising system cause higher drug blood levels which are associated with neuropsychiatric adverse drug reactions (ADRs), such as akathisia. If not recognised, akathisia, which often precedes violence, suicidality, homicide, mania and psychosis, may be mistaken for new or emergent mental illness and treated with further ineffective, counter-productive psychiatric drugs.

Research limitations/implications • The absence of pharmaceutical data for CYP450 diminishing, null/non-functioning or multiple polymorphisms and variations in the 5-HTTLPR and 5-HT, linking general medications and psychiatric drugs with neuropsychiatric behavioural reactions is notable. There is limited information linking psychiatric drug disruption of homeostasis and neurotransmitters with violence. These issues indicate a need for greater pharmaceutical transparency and further research into the role of CYP450, 5-HTTLPR and 5-HT polymorphism associated neuropsychiatric ADRs for all psychiatric drugs and serotonergic general medications.

Practical implications • Safer prescribing is important and could be achieved by individual genotype testing, which would identify persons with genetic polymorphisms, who are unable to metabolise drugs. Prevention of violence would enhance peoples' well being, ground floor practitioner and public safety.

Conclusion • This paper is the first review that implicates certain drugs as a cause of violence due to pharmacogentic polymorphisms and neurotransmitter disruption. (*Adv Mind Body Med.* 2018;33(1):4-21.)

Corresponding author: Kelly Brogan, MD
E-mail address: drbrogan@kellybroganmd.com

INTRODUCTION

A critical appraisal of the available evidence is presented for violence in connection with people who are prescribed psychiatric and general medications.

The new generation antidepressants, Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), are prescribed both in general medicine and psychiatry. Common mental health affective disorders-e.g. depression, generalised anxiety, panic, post traumatic stress and obsessive compulsive disorders and social phobia are treated with antidepressants.[1] In general medicine physical diseases such as chronic pain, fibromyalgia, peripheral neuropathy and premenstrual dysphoric disorder

and smoking cessation,[2] are also treated with antidepressants when there is no previous history of a mental health condition.

Violent incidents may be committed *after* being diagnosed and treated for common mental health conditions and SMI. Suicide (violence towards self) and homicide (violence towards others), can be triggered by people experiencing aggression and akathisia, which can be caused by psychiatric drugs and general medications. In double-blind, randomised placebo-controlled trials, when antidepressants were given to healthy volunteer adults with no prior history of a mental condition, the occurrence of events leading to suicide and violence, doubled.[3]

Moore et al (2010) identified 1527 cases of violence, including homicides, disproportionably reported to the FDA for 31 drugs, including varenicline, eleven antidepressants, six sedative/hypnotics and three drugs for attention deficit hyperactivity disorder.[4] Even though there was no violent history prior to treatment, some people prescribed antidepressants experienced hallucinations, delusions or become suicidal.[5,6] Many general medications can cause psychiatric reactions including anxiety, depression, mania, psychosis, cognitive disturbance and delirium.[7] whilst others can induce suicide and homicide ideation.[8]

In the 1950s people diagnosed with "severe mental illness" (SMI), schizophrenia or bipolar, were treated with major tranquillisers such as stelazine, haloperidol and chlorpromazine which are now classified as "typical antipsychotics".

From the late 1980s, people were treated with the newer generation "atypical antipsychotics". Although violence is associated with alcohol and/or recreational drugs when used in conjunction with the newer generation of "atypical antipsychotics", some people prior to SMI diagnosis have no history of violence, neither have they used alcohol or recreational drugs during neuroleptic treatment and yet still experience violence.

Some 40% of the population have pharmacogenetic CYP450 polymorphisms and 42% Caucasians have the *s (short)* variant of the 5-HTTLPR, impeding efficient metabolism of some general medications and psychiatric drugs. This together with the concurrent disruption of neurotransmitters and homeostasis induces behavioural changes. Thus populations with pharmacogenetic CYP450 polymorphisms and 5-HTTLPR variants prescribed a general medication can incur a common mental health diagnosis which, when treated with psychiatric drugs, can induce violence leading to a diagnosis of SMI.

For clarification psychiatric "drugs" is the preferred terminology in this review as opposed to medication. The latter term applies solely to diseases that are scientifically proven, which is not the case in psychiatry. The term 'antipsychotic' was coined as a marketing ploy by drug companies to replace 'major tranquillisers' and neuroleptic terminology. Neuroleptic is a more accurate term being described by Delay and Deniker in 1955 for chlorpromazine "…because of the drug's capacity to "seize"(leptic) the brain (neuro) in the same manner as several neurological disorders…" [9] and is therefore used in this review.

Akathisia

Akathisia is an extrapyramidal side effect (EPSE), a neuropsychiatric behavioural reaction, initially described in 1901 by neuropsychiatrist Ladislav Haskovec, and was associated with hysteria.[10] Nervous conditions in asylums were treated extensively with potassium bromide that caused tremor side effects and were likely to be the true nature of akathisia.

In the late 1950's to 1970's akathisia was formerly recognised and is related to high psychiatric drug doses, rapid increases or changes in dose[11,12] either up or down. The response to toxic levels of psychiatric drugs and alterations in drug blood levels causes neuropsychiatric behavioural disturbances, which are idiosyncratic and can stem from pharmacogenetics. Akathisia symptoms include dysphoria,[11,13] and 'an inner agitation or jitteriness that is usually (but not always) accompanied by an inability to sit still or stop moving. It is sometimes described as psychomotor agitation or restless leg syndrome. Difficulty with diagnosis may be compounded by the condition being intermittent, and the absence of external physical movements at the time the patient is being observed. Careful questioning will elicit akathisia even though internal sensory dissociation is present.'[14] Alternative clinical diagnosis may include anxiety, depression, agitation, exacerbation of psychosis or other psychiatric diagnoses.[15]

'The state causes heightened irritability and frustration with aggression against self or others, and often a generally worsening of the mental condition.'[16] Hallucinations, psychosis, depersonalization, abnormal thinking and delirium are symptoms which sometimes result from a superimposed toxic state,[16] i.e. a toxic psychosis. When experiencing akathisia, a person is prone to respond violently to perceived insult, provocation or "psychological blow" being less able to cope with disrespectful attitudes from others.

The rates of akathisia increased when typical neuroleptics were prescribed,[10] with acute akathisia rates ranging from 8% to 76%.[13] The new generation atypical neuroleptics were thought to cause less EPSEs and were promoted as such, although akathisia rates remained high, up to 39% after their introduction in the late 80s.[17,18,19] The reported prevalence of akathisia among individuals receiving neuroleptic drugs has varied widely (20%-75%);[20] this may be due to a lack of consistency in the definition of caseness, neuroleptic prescribing practices, study design, and the demographics of the population being studied. Consequently, this factor is associated with overlooking the diagnosis of akathisia with atypical neuroleptics.[21] Acute akathisia tends to persist for as long as neuroleptic drugs are prescribed, although the intensity may fluctuate over time; a rating scale for akathisia, therefore may be different from one day to another and therefore unreliable as a diagnostic tool.

Table 1. Akathisia related toxic behavioural ADRs: typical neuroleptics[14,22,23]

Typical Neuroleptics	Neuropsychiatric Reactions
Clopixol	agitation, akathisia
Haloperidol	restlessness, agitation, akathisia
Trifluoperazine	akathisia, restlessness
Sulpiride	restlessness, akathisia

Table 2. Akathisia related toxic behavioural ADRs: atypical neuroleptics[23,24,25]

Atypical Neuroleptics	Neuropsychiatric Reactions
Aripiprazole	restlessness, agitation, akathisia, aggression
Amisulpride	restlessness, agitation, akathisia, aggression
Clozaril	akathisia, agitation, aggression, disruptive behaviour, restlessness
Olanzapine	akathisia, restlessness, agitation
Palperidone/invega	akathisia, aggression, anxiety, agitation, mania, restlessness
Quetiapine	Akathisia, irritability, restlessness, suicidal ideation and suicidal behaviour
Risperidone	akathisia, restlessness agitation anxiety
Sertindole	akathisia

Akathisia was found to be the predisposing factor in 50% of violent incidents during neuroleptic treatment.[26] Both typical and atypical neuroleptics are associated with violence,[22,27] suicidal and homicidal behaviour,[28] suicide,[14,29] and homicide.[14] In five case histories depicting homicide and suicide, all patients had akathisia prior to the events, elicited by careful questioning as external signs were not visible.[14]

Many epidemiological studies demonstrate that people being treated for SMI have deteriorating outcomes in mental health; deaths, violence, and suicides have increased up to 20-fold since 1924.[29-33] People with the diagnosis of schizophrenia have higher rates of suicide compared with the general population,[31] with a 4 to 6 fold increased risk of violent behaviour.[34] In placebo-controlled trials excess suicides in psychosis are linked solely with neuroleptics.[35]

Antidepressants

When the new generation antidepressants were introduced in the mid 1990s, akathisia became prominent.[11,13,36] Akathisia is a recognised ADR occurring with SSRIs and SNRIs.[2,13,37] The DSM-IV-TR states akathisia can be associated with dysphoria, irritability, aggression or suicide attempts, behavioural dyscontrol,[38] severe anxiety, peculiar bodily sensations, bizarre thinking and reasoning.[39] Antidepressant induced akathisia worsens mental stability, being connected with violence,[2,3] suicide ideation,[40-43] suicide attempt,[44,45] homicidal ideation[43] and homicide.[46] Despite Eli Lilly denying suicidality and violence as ADRs resulting from prozac, the company has paid out millions of dollars to survivors and victims of suicide and murder.[47] The initial treatment stage appears to be connected with the most risk of suicidality and similarly to akathisia, is linked with a dose increase and sudden, rather than slow, cessation withdrawal.[2]

A data review disclosed '…possible doubling of the relative risk of both suicides and suicide attempts on SSRIs compared with older antidepressants or non-treatment, make it difficult to sustain a null hypothesis, i.e. that SSRIs do not cause problems in some individuals to whom they are given.'[48] The risk of suicide was up to four times higher with SSRIs than placebo and 'The claims to greater safety have been discredited by evidence of drug-induced violence occurring among SSRI patients at rates which greatly exceed older [antidepressant] drugs and placebo.'[49]

Other neuropsychiatric reactions connected with antidepressant drugs: venlafaxine, marketed as a SNRI, can cause hysteria, impulse control difficulties, paranoid reaction, psychotic depression,[43] mania/euphoria, hallucinations, aggression and delirium.[50] SSRIs paroxetine,[51] citalopram[52] fluvoxamine[53] and sertraline[54] and SNRI duloxetine[55] are linked with mania. Paroxetine can also induce hallucinations.[51] Any of the above iatrogenic neuropsychiatric reactions may contribute to suicidal and/or homicidal behaviour.

Mania and psychosis were reported in Eli Lilly internal documents for prozac; these ADRs were presented by Los Angeles lawyers, Baum Hedland at the Forsyth v. Eli Lilly Trial in 2006 having been with held from the public by Eli Lilly since 1984.

In a fourteen month period between 1997 and 1998 a survey in Connecticut found 43 (8.1%) of 533 hospital admissions were patients prescribed antidepressant medication experiencing psychosis or mania. The survey concluded '...the rate of admissions due to antidepressant associated adverse behavioural effects remains significant.'[56] When no mania or psychosis is in evidence before psychiatric drugs have been prescribed it becomes clear these neuropsychiatric reactions are iatrogenic.

In antidepressant clinical trials, akathisia has been miscoded as, "agitation, emotional lability and hyperkinesis (over activity)"[2] SmithKline Beecham, now GlaxoSmithKline, as opposed to using akathisia, which is coded as akathisia in the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART), preferred to use their own coding for akathisia such as "agitation, anxiety, stimulation, nervousness, and tremor" in paroxetine drug trials.[57] Recently COSTART has been replaced by MeDRA, the Medical Dictionary for Regulatory Activities. In clinical trial data the code words for suicidal ideation are emotional lability/mood swings,

homicidal ideation is coded as hostility and EPSE is usually called behavioural dyscontrol or behavioural toxicity.

Akathisia is entirely unrelated to psychiatric diagnosis as it is a reaction to chemical toxicity. The FDA advisories clearly state: "Anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. "Although FDA has not concluded that these ADRs. are a precursor to either worsening of depression or the emergence of suicidal impulses, there is troubling concern that people who experience one or more of these ADRs may be at increased risk for worsening depression or suicidality. In these circumstances drug therapy should be evaluated, and treatment may need to be discontinued when symptoms are severe, abrupt in onset, or were not part of that person's initial distress. Some people taking psychiatric drugs develop akathisia and some people who develop akathisia kill themselves or others.

Dysphoria may or not be associated with akathisia[58] and is defined as an "…extremely unpleasant and distressing subjective change in mood."[59] Dysphoria has been linked with a high rates of suicide in the first year of neuroleptic treatment[35] and needs to be recognised in order to prevent a worsening state of mental health.

Whatever the prescribing reason for new generation of antidepressant drugs, some people will experience ADRs such as akathisia, violence, suicide or homicide. Because akathisia is under diagnosed[21] and often misconstrued as an 'uncovered" mental illness or an intractable mental illness,[60] it's recognition is essential to safe guard against worsening mental stability and for the safety of other people in the community or hospital.

Withdrawal From Psychiatric Drugs

Withdrawal from psychiatric drugs can be incredibly difficult due to potential emergent withdrawal neuropsychiatric behavioural reactions, including akathisia. For example, benzodiazepine withdrawal can cause anxiety and confusion; lorazepam and oxazepam, with a shorter half-life, carry risk of toxic psychosis, or a condition resembling delirium tremens on withdrawal.[61] MIND, mental health charity, reports neuroleptic withdrawal can cause restlessness, irritability and agitation, which are akathisia symptoms. Akathisia is associated with SNRI withdrawal.[62] SSRI withdrawal effects include irritability,[63,64,65] agitation,[65] EPSE,[66] akathisia,[62,67] aggression[53] and risk of suicidality.[2] Withdrawal psychosis is linked with prozac treatment.[47] The older generation monoamine oxidase inhibitor and tricyclic antidepressant withdrawal symptoms include EPSE,[66] akathisia,[62] and hypomania/mania.[68,69]

Withdrawal effects may be mistaken for a relapse.[70] Although relapse predictors rate levels of akathisia and EPSE,[71] these symptoms need to be acknowledged as neuropsychiatric behavioural reactions as opposed to a state of mental illness. Being fully aware of persons' perpetual internal agitation and heightened irritability, having respectful behaviour and attitudes in relationship with people is paramount to prevent verbal and physical aggression.

Medications Used For Physical Diseases

The following table depicts eighteen classes of general medications some of which are also associated with Serotonin Syndrome (see Table 8), that can induce toxic neuropsychiatric ADRs.

Table 3. General medications associated with toxic neuropsychiatric reactions.

Drug Class	Name	Neuropsychiatric Reactions
Acne medication	isotretinoin: accutane	Suicide, psychosis, depression[72]
	isotretinoin: roaccutane	Suicidal ideation, depression, aggressive behaviour, anxiety, psychosis[61]
	azithromycin	Anxiety, sleep disturbances, agitation
	clarithromycin	Insomnia, nightmares, anxiety, psychosis
	telithromycin	Insomnia, nervousness, hallucinations[61]
Anaesthetic	triflupromazine	Extreme akathisia[73]
Angina and Hypertension	calcium channel blockers	Sleep disturbances, mood changes, tremor, EPSE, anxiety, depression[61]
	beta blockers	Sleep disturbances with nightmares, psychoses, depression[61]
	peripheral vasodilators	Insomnia, abnormal dreams, anxiety, agitation, sleep disturbances[61]
	ACE inhibitors	Sleep disorder, dream abnormalities, insomnia, nervousness, depression, anxiety, mood changes, tremor[61]
	Ranolazine	Tremor, anxiety, hallucinations[61]
Antibiotics	quinolones	*Restlessness,[74] anxiety, depression, hallucinations, tremor, psychoses[61 BNF]
	levofloxacin	see quinolone effects includng: abnormal dreams, EPSE
	nalidixic acid	see quinolone effects includng: toxic psychosis[61]
	cephalosporins	Hyperactivity, nervousness, sleep disturbances, hallucinations[61]
	carbapenems: ertapenem	Anxiety, depression, agitation, tremor, hallucinations[61]
	carbapenems: metronidazole	Psychotic disorders[61]

Table 3. (continued)

Drug Class	Name	Neuropsychiatric Reactions
Anti-eleptic drugs	carbamazapine (tegretol)	Suicide risk, suicidal ideation, latent psychosis, confusion, agitation, hallucinations (visual or auditory), depression, aggression, restlessness, irritability, confusional state, insomnia [24]
	lamotrigine	Suicidal ideation and behaviour, aggression, irritability, confusion or agitation, hallucinations, extrapyramidal effects[24]
	gabapentin	Suicidal ideation and behaviour, hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal, agitation, mental impairment[24]
	phenytoin	Suicidal ideation and behaviour, increasing irritability, mental confusion, dyskinesias, tremor, insomnia[24]
	topiramate	Suicidal ideation and behaviour, see also carbamazapine effects including: anxiety, mood swings, anger, abnormal behaviour, affect lability, paranoia, panic attack, tearfulness[24]
	sodium valproate – epilim	Suicidal ideation and behaviour; see also carbamazapine effects including: extrapyramidal disorder[24]
Anti-emetic	prochlorperazine	Akathisia, EPSE, tremor, neuroleptic malignant syndrome (NMS), agitation, excitement, insomnia[61]
	droperidol	proclorperazine effects including: anxiety, hallucinations[61]
	domperidone	see prochlorperazine effects including: anxiety[61]
	metoclopramide	see prochlorperazine effects including: suicide attempt[75]
Anti-fungals	voriconazole	Anxiety, depression, agitation, insomnia, hallucinations, tremor.[61]
	griseofulvin	Sleep disturbances, agitation, depression[61]
Anti-histamine	non sedating: loratidine	EPSE, depression, sleep disturbances, tremor
	non sedating: rupatadine	see loratidine effects including: irritability
	non sedating: desloratidin	see loratidine effects including: hallucinations[61]
	sedating: promethiazine	EPSE, depression, insomnia, tremor, akathisia, Neuroleptic Malignant Syndrome (NMS), agitation, excitement[61]
	sedating: chlorphenamine	see promethiazine effects[61]
	sedating: cyproheptadin	see promethiazine effects[61]
Anti-malarial	mefloquine	Suicidal ideation, suicide, psychosis, tremor, abnormal dreams, insomnia, acute anxiety, restlessness, depression.[61]
	chloroquine	ESPS[61]
	proguanil with atovaquone (malarone)	Abnormal dreams, depression, anxiety, hallucinations[61]
Anti-parkinson	monoamine-oxidase-B inhibitors: selegilene	Depression, psychosis, tremor, movement disorders, sleeping disorders, agitation, anxiety[61]
	levodopa: madopar	Suicidal ideation, EPSE, psychosis, euphoria, abnormal dreams, insomnia, depression, anxiety, agitation, NMS, compulsive behaviour.[61]
	dopamine agonists: pergolide (ergot)	Hallucinations, compulsive behaviour, impulse control disorder (ICD)[a]
	dopamine agonists: pramipexole (non-ergot)	Hyperkinesia, hallucinations, restlessness, compulsive behaviour, ICD,[a] delusion, paranoia[61]
Anti-smoking	varenicline	Suicidal ideation, sleep disorders, abnormal dreams, depression, anxiety, hallucinations, panic attack, mood swings, tremor, restlessness, aggression, irrational behaviour, psychosis, sleep-walking, agitation[61]
	bupropion	Suicidal ideation, agitation, anxiety, depression, insomnia, tremor, abnormal dreams, hallucinations, hostility, irritability, aggression, delusions, paranoid ideation, restlessness[61]
Antitussives (cold remedies)	Pseudoephedrine (sudafed)	Anxiety, restlessness, hallucinations[61]
Benzodiazepine	midazolam	Hallucinations, paradoxical excitement and aggression[61]
	diazepam, lorazepam & alprazolam	Aggression, hostility, anxiety, talkativeness and excitement, aggressive and antisocial acts.[61]
Cholesterol lowering drugs	Statins	*Sleep disturbance, depression[61] aggressive or violent behaviour[76]
	simvastatin	see statins effects
	atorvastatin	see statins effects
	mevastatin	see statins effects including: anxiety[77]

Table 3. (continued)

Drug Class	Name	Neuropsychiatric Reactions
Corticosteroids	glucocorticoid betamethasone dexamethasone hydrocortisone prednisolone	Suicidal thoughts, serious paranoid state or depression with risk of suicide, nightmares, insomnia, irritability, mood lability, corticosteroid-induced psychosis[61]
Inhaled Cortico-steroids	used in asthma and COPD (chronic obstructive pulmonary disease)	Anxiety, depression, sleep disturbances, behavioural changes including hyperactivity, irritability, aggression (particularly in children) [61]
Hypnotics	zaleplon	Depression, hallucinations, hostility, aggression, sleep-walking[61]
	zolpidem	see zaleplon effects includng: agitation, nightmares[61]
	zopiclone	see zaleplon effects includng: nightmares[61]
	clormetiazole	Paradoxical excitement[61]
Indigestion and Acid Reflux	proton pump inhibitors: (PPIs)	Sleep disturbances, depression, hallucinations, confusion[61]
	omeprazole	see PPI effects including: irritability,[78] agitation,[61] aggressive behaviour[79]
	lanzoprazole	see PPI effects including: restlessness[61]
	H_2 antagonists imetidine/ tagamet ranitidine/zantac	Psychiatric reactions: confusion, depression, hallucinations
Opioid Analgesics	tramadol	Hallucinations, dysphoria, mood changes, depression, sleep disturbances[61]
	buprenorphine	see tramadol effects including: agitation, anxiety, restlessness, tremor, psychosis[61]
Miscellaneous	Tamiflu (oseltamivir)	Agitation, abnormal behaviour, anxiety, confusion, delusions, delirium, hallucination, insomnia, nightmares, self-injury or fatal outcomes[24]

[a]Treatment with dopamine-receptor agonists and levodopa is associated with impulse control disorders, (ICD),[61] characterized by "problems in emotional and behavioural self-control"[80] and failure to resist a temptation, urge or impulse that may harm oneself or others.

Table 4. Outline of the differences between mental states due to toxicity and functional psychoses

Mental States Due To Toxicity	The Functional Psychoses
Toxin, substance or psychiatric drug in use or recently used.	All "functional psychoses" carry the exclusion, *"not caused by substance or medication"*
• Akathisia, restlessness, obsessive preoccupation with death, dying and suicide. • Inexplicable impulse to kill people one most loves, violence, behavioural dyscontrol, confusion/ambulant delirium, manic shift. • Confusion misidentification • Weird violent dreams, insomnia • Hallucinations • Sick, vomiting, tachycardia, loss of coordination, cognitive impairment and memory problems. • Confabulations, shifting false reports, misinterpretation, serotonin toxicity or neuroleptic malignant syndrome.	• Clear mind • Absent: confusion. • Absent: physical / neurological disease. Absent: substance/ medication use. • Absent: causation. • Specific voice hallucinations, rare if ever visual • Fixed delusions, correctly defined. • Mania or depression.
Prominent: confusion, lack of coordination memory/cognition impaired.	Absent: confusion, lack of coordination, otherwise clear thinking.

Personal communication: Dr Yolande Lucire, PhD, MBBS, DPM, Forensic & Medico-Legal Psychiatrist. 26th Feb 2014.

The above list is not inclusive of all the general medications that cause toxic neuropsychiatric reactions. In brief medications that have akathisia, also miscoded as agitation, emotional lability and hyperkinesis, among their side effects are capable of inducing suicidality and violence.

Toxic and Functional Psychosis

Critical toxic behavioural changes induced by general medications can be mistaken for a new mental health diagnosis. Similarly side effects of recreational substances may lead to a mental health diagnosis from the unwary clinician. In the presence of drug or medication induced neurotoxic behavioural effects, failure to clarify that these neuropsychiatric reactions are not related to, nor evidence of a psychiatric diagnosis, is disregarding the DSM criteria which 'stipulate an exclusion that the diagnosis to be made is not caused by a substance, a medication, or other treatment.'[81] ICD-10, the World Health Organization (WHO) official diagnostic system used in the UK by those who code hospital admissions, also differentiates between mental states due to toxicity and mental illnesses. When a person has been prescribed neuroleptics, supersensitivity psychosis depicted by delusions and hallucinations supervenes[82] confounding the diagnostic skills of all but the most enlightened psychiatrists, who are aware of iatrogenic behavioural changes.

The Magnitude of Violence and Psychiatric Inpatient Deaths

The connection between violence, including suicide,[83] and people diagnosed with a mental health condition has

been verified by many studies.[84,85] Suicide has been linked with akathisia since the 1950s[46] when typical neuroleptics, such as fluphenazine[86] and haloperidol[14] were introduced.

From the late 1980s violence and suicide tended to rise again[29,31] which coincided with the introduction of new generation antidepressants associated with iatrogenic akathisia. Between 2000-2009, out of the 1829 New Zealanders taking antidepressants, 39% experienced suicidality.[87] In 2006, a survey in Sweden found 71% women and 48% men who committed suicide had received one or more psychiatric drugs in the categories of antidepressants, neuroleptics, hypnotics/tranquilizers; in total (55%) of all the persons who committed suicide within a year had received treatment with psychiatric drugs in one or more of these classes.[6] The number of people under mental health care in the UK has risen, and correlates with the rise of suicides.[88] Between 2004-2014 there were 18 172 suicides by people who had accessed mental health services in the previous 12 months, accounting for 28% of suicides in the general population.[88] In 2014 alone, 460 suicides in the UK, were by people within a psychiatric milieu, either as inpatients, in acute care, post-discharge care or with crisis teams.[88]

In 2014, there were 209 deaths of patients detained under the Mental Health Act in England and Wales.[89] However, the exact current number of adult in-patient deaths in the UK, whether self inflicted or by so called 'natural causes' remains unknown due to the absence of legal requirement for Health Trusts' to report them; some Health Trusts report deaths, whilst others abstain from reporting. This situation also applies to learning disability deaths in mental health settings.[90] In comparison, deaths in other detention settings are legally notifiable with the facts made known to the public. Additionally, because the UK's Care Quality Commission and Healthcare Inspectorate Wales stipulated the removal of figures for deaths that occurred whilst subjected to legal Community Treatment Orders or Guardianship, these mental health death related figures have not been recorded and are therefore also unknown.[89] Moreover, there is no legal obligation in England and Wales to record or investigate child in-patient deaths when receiving mental health care. [91]

Even though the removal of potential ligature points in hospital settings helped to reduce inpatient suicides by 60% from 2004-2014, there were 200 suicides in the community in 2014, three times as many suicides compared with 76 suicides in hospital.[88] People in hospital with akathisia and the compulsion to commit self-violence in hospital may be thwarted, but this compulsion does not spontaneously disappear when discharged to the community, and is the likely explanation for the high suicide risk in the three months post hospital discharge period.

Homicide has been linked with akathisia since 1985.[46] In the UK from 2004-2014 there were 870 homicides, 11% of the total population, by people diagnosed with mental health conditions. These included schizophrenia, other delusional disorders, personality disorder and common affective disorders such as depression and generalised anxiety. [88]

However, similar to the inaccurate suicide statistics, this is not an accurate representation of people who had been receiving psychiatric drugs and committed homicide; "The Home office does not collect data on people who have committed homicide and whom have been in contact with mental health services." (Personal Communication: Katherine Piedrahita, Crime and Policing Analysis, Home Office Analysis and Insight. 8th Nov 2017).

The common denominator for suicide and homicide is the likelihood of treatment with new generation antidepressants or atypical/typical neuroleptics, which incur akathisia, compelling people to commit violent acts.

Admission to Psychiatric Intensive Care Units (PICU) is commonly due to aggressive behaviour[92] and in three acute psychiatric units in Australia, 58% of all incidents were violent with agitation preceding incidents.[93] Aggression rates almost tripled with some prison inmates who were prescribed neuroleptics to control aggression.[94] It is possible in all three situations akathisia was a precursor to aggression.

In an attempt to address psychiatric violence in the UK, the NHS National Institute for Health and Clinical Excellence (NICE) has a full clinical guideline: *Violence. The short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments.*[95] This guideline addresses many issues, however, it does not address akathisia and the role of pharmacogenetics in CYP450 metabolism for psychiatric drugs /general medications, cannabis and other recreational drugs, nor iatrogenic neurotransmitter disruption.

Pharmacogenetics

Pharmacogenetics determines each person's functional ability to metabolise or break down drugs. The first phase of metabolism is through the genetically diverse Cytochrome CYP450 enzymes; each CYP450 gene consists of two strands of DNA from each parent and has a variety of polymorphisms (variations). Extensive metabolisers (EMs) are known as "normal" efficient metabolisers, with drugs being therapeutic and without the toxicities that incur ADRs. Poor metabolisers (PMs) are inefficient metabolisers with no functional metabolising activity; the resulting drug/medication toxicities cause ADRs. Intermediate metabolisers (IMs) have diminished activity and are at greater risk as ADRs build up slowly taking time to appear. Ultra rapid metabolisers (UMs) have multiple allele copies with increased function; this higher than normal rate of metabolism results in treatment being inefficient or, with prodrugs, results in high levels of prodrug toxic metabolites, causing rapidly occurring ADRs. Persons who are PMs and/or IMs of psychiatric drugs and general medications, and UMs of prodrugs experience neurotoxic behavioural reactions and treatment failure due to sub-optimal metabolism.

"Antidepressants, antipsychotics, antiarrhythmics, antiemetics, beta-adrenoceptor antagonists (beta-blockers)

Table 5. The link between genotype status and neurotoxic ADRs for CYP450, 5HTT-LPR and 5-HT allele variants when treated with antidepressant drugs.

Neurotoxic Behavioural ADRs	CYP450 And Serotonergic Genetic Variants
Akathisia/agitation/restlessness	CYP450 2D6 and 2C19 non-functional alleles[46] CYP450 2D6 and 2C9 diminished function alleles[46] CYP450 2C19 ultra rapid multiple allele duplications[46] CYP2C9 non-functional alleles[111] 5-HTTLPR short allele [112,113] 5-HTR2A receptor variant [114]
Suicide/suicide risk	CYP450 2D6, 2C19 and 2C9 non-functional and diminished function alleles.[46,111] CYP450 2D6 ultra rapid multiple allele duplications [46] 5-HT1AC receptor variant[115]
Homicide/attempted homicide	CYP450 2D6 and 2C19 non-functional[46] CYP450 2D6 and 2C9 diminished function alleles[46] CYP450 2C19 ultra rapid multiple allele duplications[46]
Insomnia	5-HTTLPR short allele[112]

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Serotonin Syndrome	CYP450 2D6 IM[117]
Psychosis	CYP2D6 non-functional and diminished allele[111]
Delusions	CYP2D6 diminished allele[111]
Dysphoria	CYP2D6 non-functional allele and diminished function allele[111]
Hallucinations	CYP2D6 non-functional allele and diminished function allele[111]

and opioids" are metabolised by CYP450 2D6,[96] with 75% of psychotropic drugs[97] and 25% of general medications[98] metabolised by CYP450 2D6.

CYP450 2C9 and 2C19 metabolise proton pump inhibitors, certain tricyclic antidepressants, barbiturates, beta-blockers, non-steroidal anti-inflammatory medications and warfarin.[99] One single neuroleptic, such as clozapine requires a combination of CYP450 1A2, 3A4, 2C9, 2C19, 2D6 enzymes for metabolism.[100] The metaboliser status or phenotype of the individual, for the CYP450 system is determined by many factors including the co-prescription of cytochrome inhibiting medication/drugs, iron status, general and liver health.

Population Frequency of Genetic Variations

CYP450 2D6 is a highly variable enzyme in different populations. CYP450 2D6 PMs prevalence: Caucasians (5-10%),[101,102] Asian (0-2%),[102] African (6.3%),[103] African American (14.5%),[103] and Black populations up to 19%.[102] East Asians (50%),[103] and Pacific Islanders (41%),[103] have the diminished CYP2D6*10.[102,103] Up to 29% in North Africa and the Middle East, are CYP2D6 UMs.[101]

CYP2C19 PM prevalence: Europeans (3-6%),[104] Asians (41%),[105] and East Asians (up to 25%).[101] Melanesian populations (up to 90%) PMs[105] and persons from Vanuatu have a 79% rate of the diminished 2C19*2.[104]

ADRs can occur with just one non-functional or one diminished function allele. For example, CYP1A2*1C, diminished function and CYP1A2*1D (ultra rapid) are associated with increased clozapine exposure and adverse reactions.[106] Risperidone and CYP2D6 diminished function allele is associated with NMS.[107] It is important to note that ADRs are substrate specific in that an IM genotype enzyme at CYP2D6 will become a PM phenotype when a drug that is an inhibitor of CYP2D6 is used.[108]

The CYP1A2*1K allele has diminished induction.[109] In 3 case studies, Asian patients prescribed clozapine experienced aggression and disruptive behaviour which improved when clozapine was discontinued.[25] Although the genotype of the Asian patients in the study is unknown, 25% of Asians[110] have CYP1A2*1C diminished induction and 41% are non functional at 2C19*2 or 2C19*3.[105] It is possible the patients had a combination of CYP450 diminished or non-functional genotypes which could have predisposed these patients to disruptive behaviour when treated with clozapine.

"All antidepressants are metabolized by the enzymes CYP2D6, CYP2C19, CYP3A4 and CYP1A2 to varying degrees, [*depending on metaboliser status*], with the first three contributing most to metabolism" [46] Norfloxetine, the first metabolite of Prozac (fluoxetine) is psychoactive and is metabolized by CYP2C9, so 2C9 is just as important as 2D6 which can be quickly inhibited. In Nordic Caucasians, non-responders to antidepressant therapy were found to have a 10-fold higher incidence of CYP2D6 gene duplication compared with healthy volunteers.[118] In a study of drug intoxication as a cause of death, Zackrisson found in a higher number of suicide cases there was a higher number carrying more than two active CYP2D6 alleles as compared with

those who died of natural-death.[118] Moreover UMs at CYP2D6 were over represented in the morgues as suicides and intoxications deaths.[118] Neuroleptics have similar metabolising pathways to antidepressants,[119] so persons with genetic variations will experience toxic behavioural changes similar to antidepressant ADRs.

Cannabis is predominantly metabolised though CYP450 3A4, 2C9, 2C19 and 2D6[120,121,122] and 50% of cannabis smokers who have accessed drug clinics have the heterozygous genotype of cytochrome P450 2D6*4,[122,123] a PM phenotype.

Persons who take recreational drugs and have pharmacogenetic variations in these enzymes are susceptible to neurotoxic changes in their mental state. Reported behavioural reactions from cannabis use include hallucinations, paranoia,[131] psychosis,[132] volence,[133,134] and suicide.[135] Homicide[136] is reported from a variety of recreational drugs. Methamphetamine and cocaine can cause paranoid reactions and violence.[16] Withdrawal symptoms from recreational drugs include aggression and/or irritability[131] which are symptoms of akathisia.

Users who have an inability to metabolise recreational drugs, will not be able to metabolise psychiatric drugs efficiently either if prescribed in an attempt to ameliorate toxic induced mental status changes. The likelihood of further akathisia, treatment emergent suicidal ideation and violence towards others followed by diagnosis with SMI is inevitable.

Polypharmacy

Polypharmacy can cause drug-drug interactions due to psychiatric drugs or medications either inhibiting or inducing metabolism[137] via the CYP 450 enzymes and prescribers need to be aware of interactions that can worsen behavioural reactions.[138] For example a variant of NMS secondary to drug interaction was incurred when donepezil was added to olanzapine with a patient already experiencing EPSE.[139] Omeprazole, proton pump inhibitor prescribed for gastric reflux, a common side effect of neuroleptics, is a CYP1A2 inducer.[138] When omeprazole was concurrently prescribed with clozapine the interaction caused a significant reduction of plasma clozapine levels,[140] which effectively causes an unwanted psychotic withdrawal reaction with the associated akathisia and potential violence.

Six case studies involving antidepressants and psychiatric polypharmacy and two case studies involving antidepressants and psychoactive agents resulted in homicide and attempted homicide.[46] SSRIs and other antidepressants that are serotonergic agents have effects upon serotonin receptors or serotonin uptake.[49] Deletion of long alleles in 5-HTT is associated with a 'powerfully predicted non response',[141] and more adverse events with paroxetine.[142] The 5-HTTLPR short allele is associated with akathisia, insomnia, mania and delirium,[142] agitation[112,113] and anxiety.[113]

Allelic variation in the HTR2A gene has been reported to affect response to SSRIs and risk for adverse drug reactions, with paroxetine inducing agitation.[114]

The most common causes of intoxication were antidepressants (56.9%), analgesics (18.5%), and cardiologic drugs (10.8%), all linked with a suicide risk.[115]

Genotyping for Patient Safety

Although genotyping plays an important role in protecting persons from iatrogenic psychiatric behavioural harm, genotype testing is largely unknown to the UK's medical profession, despite different rates of metabolism being associated with distinctive responses for over 50 years.[143]

Table 6. Metabolic pathways of recreational and psychiatric drugs show the same CYP450 pathways are used.[121,124-130]

	CYP450 Enzymes				
Recreational Drug	**1A2**	**2D6**	**2C9**	**2C19**	**3A4**
Cocaine	Inducer	Substrate Inhibitor	Inhibitor		Substrate Inducer/ Inhibitor
methamphetamine		Substrate Inhibitor			
MDMA, (Ecstasy)	Inducer	Substrate Inhibitor[a]			Substrate
Cannabis	Substrate	Substrate	Substrate	Substrate	Substrate
Atypical Neuroleptic	**1A2**	**2D6**	**2C9**	**2C19**	**3A4**
Olanzapine	Substrate	Substrate inhibitor	Inhibitor	Inhibitor	Inhibitor
Quetiapine	Substrate	Substrate inhibitor		Substrate	Substrate
Risperidone		Substrate			Substrate inhibitor
Clozapine	Substrate inhibitor	Substrate inhibitor	Substrate inhibitor	Substrate inhibitor	Substrate inhibitor/ inducer
SSRI	**1A2**	**2D6**	**2C9**	**2C19**	**3A4**
Fluoxetine	Substrate inhibitor	Substrate inhibitor	Substrate inhibitor	Substrate inhibitor	Substrate inhibitor
Paroxetine	Inhibitor	Substrate inhibitor[a]	Substrate inhibitor	Inhibitor	Inhibitor
Sertraline	Substrate	Substrate inhibitor[b]	Substrate inhibitor	Substrate inhibitor	Substrate inhibitor
Typical Neuroletic	**1A2**	**2D6**	**2C9**	**2C19**	**3A4**
Chlorpromazine	Substrate Inhibitor/inducer	Substrate inhibitor			Substrate inducer

[a]strong inhibitor
[b]intermediate inhibitor

Different rates for antidepressant metabolism has been documented for several decades[143] and genotype status can be utilised in tailoring antidepressants to the individual for therapeutic efficacy in CYP2D6 and CYP2C19 dependent metabolisers.[144] Screening for 5-HTT variations determines peoples' response to SSRIs[145] and Schillevort found neuroleptics increased the risk of EPSE in persons who were CYP2D6 PMs, recommending a reduction in dosage.[146] Sweden and America have facilities for psychiatrists to screen for genetic polymorphisms in CYP2D6 and 2C19 prior to prescribing antidepressants.[97]

Clinicians' naivety about genetic status affecting drug outcomes stems initially from pharmaceutical companies' omission to specify the drug dosage for different metaboliser rates in the Summary of Product Characteristics (SmPCs). Consequently, prescribers assume all persons can metabolise the standard dosage, which is based upon EMs. Following on from drug companies' covertness, personal communication with various UK public health bodies exposed a raft of responses that adds to doctors' obliviousness to genotyping.

Doctors primarily derive their drug knowledge from the BNF, which includes SmPC data. The BNF is co- published by the Royal Pharmaceutical Society and the British Medical Association; the latter stated they have no authority to address the absence of pharmacogenetic information in the BNF. The General Medical Council (GMC) perceives pharmacogenetics as a biomedical science degree and therefore 'not in their remit.' Nevertheless the International Society of Pharmacogenomics takes a different stance recommending four or more hours of pharmacogentic teaching for undergraduate medical students; but only 21% of medical schools met that quota.[147] Some medical schools said a major concern "…regarding increased teaching in pharmacogenetics, would be the deleterious effect that this might have on other areas of the curriculum and the competing interests of other subject elements to be included in the course."[147]

Not only are medical students nearing graduation lacking in elementary genetic knowledge that is essential for patient safety in daily prescribing practice, the inadequate pharmacogenetic education at both undergraduate and postgraduate levels in UK medical schools creates an obstruction to genotyping being taken up nationally.[148,149]

According to the Care Quality Commission it is not their role to promote clinical interventions such as genotyping as they are guided by the National Institute for Health and Care Excellence (NICE). A decade ago NICE received genotype testing information via the New Ways Working for Mental Health (DH initiative); in response NICE stated genetic screening could benefit BME populations, but was not cost effective for all populations. NICE has subsequently backtracked on its responsibility towards patient safety by currently stating genotyping is 'not in their remit', despite NICE having a key role in the SmPC formulations. Furthermore, NICE specifies clinicians 'should refer to a drugs summary of product of characteristics (SPC) when considering prescribing a particular drug to a patient', (Personal communication, 24th June 2016) even though NICE are aware the standard drug dosage is problematic for persons with genetic variations. NICE now attributes the safety of medicines as the sole prerogative of the Medicines and Healthcare products Regulatory Agency (MHRA). Although the MHRA claims any new drug and any data on drug-gene interaction would be shared with NICE and the BNF, the MHRA holds no accountability for external publications.

The Royal College of Psychiatrists (RCPsych) acknowledges persons with CYP variants who take antidepressants "would be theoretically more likely to experience adverse effects, including and potentially suicidality and aggressive behaviour…" (Personal communication Professor Sir Simon Wesseley RCPsych, 2nd June 2016) and awaits research development outcomes into genetic influences on antidepressant responses. However, despite the Department of Health and Social Care investing considerably into research in the study of the genome with a view to personalising medicines, there is no published research in the UK to date depicting specific neuropsychiatric behavioural ADRs in relation with psychiatric drugs and genetic polymorphisms; neither by the Wellcome Trust, Medical Research Council nor the National Institute for Health Research.

Genotype testing is now affordable compared to a decade ago and is cost-effective.[143] The identification of people who are likely to develop neurotoxic akathisia, violence, suicide, homicide or psychosis though genotyping is essential for safe practice in prescribing.

Ethnic Black Populations

Statistically, Black Minority and Ethnic (BME) populations have greater difficulty metabolising general medications and psychiatric drugs compared with White and Asian populations. There is a higher frequency of lower metabolism at CYP450 2D6 in African Americans compared to Caucasians.[150]

Table 7. Variation of CYP450 2D6 metabolising ability in BME populations.[150,151]

BME	Poor Metabolisers	Ultra Rapid Metabolisers[a]
South Africans	18.8%	
Nigerians	8.3 - 8.6%	
Ghanaians	6%	
Black North Americans	3.3%	2.4%
Zimbabwean	2%	
Tanzanian	0.5%	
African American	3.5 - 8%	
Ethiopians	1.8%	29%

[a]UMs are at risk if the first metabolite is psychoactive.

A sample characteristics and compulsory admission report from the ÆSOP study states "…the odds of compulsory admission are 3.5 times greater for African–Caribbean male patients than for White British male patients."[152] "African-Caribbean people are three to five times more likely than any other group to be diagnosed and admitted to hospital for schizophrenia."[153]

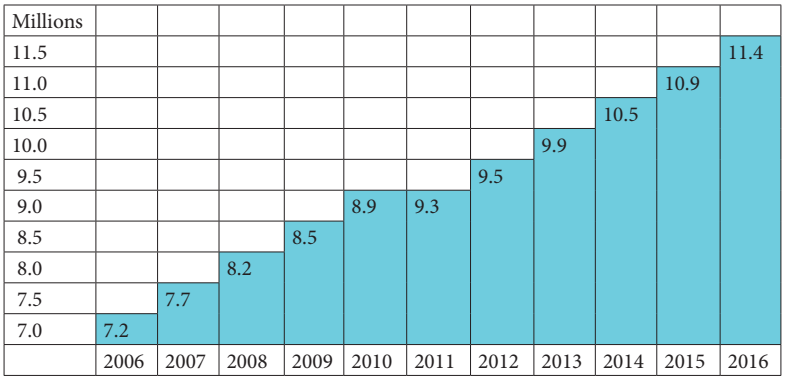
Between 2007/8 and 2008/9, the proportion of black and black British people detained rose by 9.7%. There was a rise of 9% in the number of Asian or Asian British and mixed-race people detained for treatment, compared to a 0.3% rise for the overall number of people detained. In the same year out of the 31.8% of all psychiatric inpatients detained, black/black British inpatients represented 53.9%, for mixed-race inpatients nearly 50% were detained and 40% were of Asian/Asian British inpatients.[154] The disproportionate trend for BME population detentions compared with the white ethnic group continued in 2016, with detention less likely for people in other ethnic groups.[155]

BME patients are also over represented in the UK's Psychiatric Intensive Care Units (PICUs) and Low Secure Units.[156] One study found, compared with 25.6% of total hospital admissions and 20.9% of the local catchment area population aged between 16 and 65 years, 55% of PICU admissions were from ethnic minorities.[157] "Typical PICU patients are male, younger, single, unemployed, suffering from schizophrenia or mania, from a Black Caribbean or African background, legally detained, and with a forensic history."[92]

Although the UKs Community Treatment Orders (CTOs) were introduced in 2008 to save on the expense of formal detentions in hospital, between 2008/9 and 2015/16 there was a rise of CTOs from 2,134 to 5,426 a rise of 154.2%.[158,159]

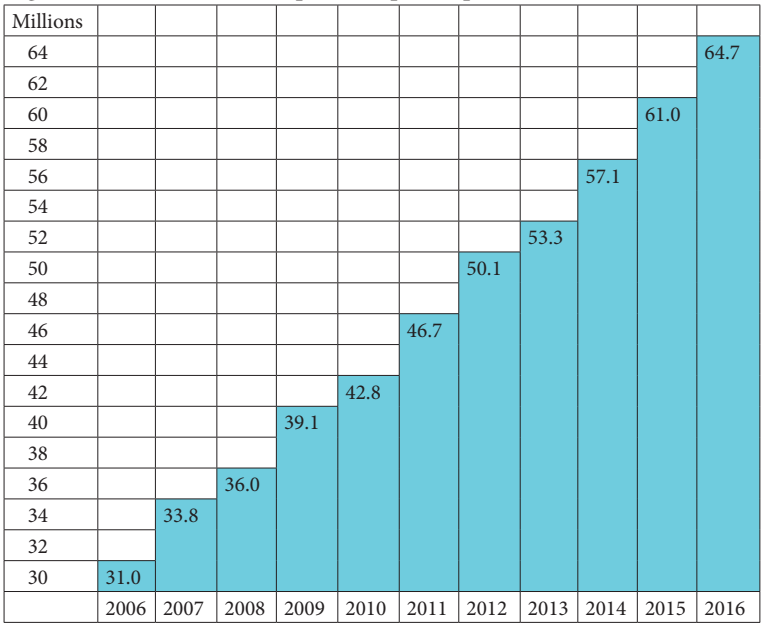
Kevin Gournay, Professor of Psychiatric Nursing, Health Services Research Department, Institute of Psychiatry, speculates on the unsatisfactory explanation between the relationship between schizophrenia diagnosis in connection with psychiatric inpatients, CTO and being black.[160] A plausible and satisfactory explanation is the higher incidence of PMs, IMs and UMs for CYP450 2D6 and 2C19 enzymes in BME populations predisposing to neuroleptic drugs causing neuropsychiatric behavioural reactions including akathisia, aggression and violence.

Figure 1. The rise in neuroleptic prescriptions.



Note: Neuroleptics used in England for psychoses and related disorders in the community[163]

Figure 2. The rise in antidepressant prescriptions.



Note: Antidepressants used in England in the community[163]

Increased Prescribing Of Psychiatric Drugs

From 2006 to 2016 in England, psychiatric drug prescriptions in the community increased to 76.1 million, an increase of 99%.[161] In the same period antidepressant prescriptions doubled to 64.7 million, surging by 108.5%, and neuroleptic prescriptions increased by 57.7% to 11.4 million.[161]

These figures do not provide the true increase for psychiatric drugs in the UK as benzodiazepines and hypnotics are not included and figures for hospital prescriptions are withheld from the public due to confidentiality issues. It is well known that visits from pharmaceutical sales representatives incur increased prescribing of all medications.[162]

Between 2015- 2016 over 2 million people approached NHS mental health services which has seen a 40% rise over the last decade.[164] One explanation for the rise in psychiatric drug prescriptions is the UK economic down turn[165] with associated austerity. Other influencing factors that would

incur increased psychiatric prescribing include the rise in the use of the UK Mental Health Act[164,166] and the rise of general medication prescriptions[163] leading to potential neuropsychiatric reactions that warrant access to primary mental health services.

Increased cannabis use[167] in populations with CYP450 and 5-HTT polymorphisms, will induce neuropsychiatric behavioural reactions, with the strong possibility of incurring a mental health diagnosis with the associated psychiatric treatment.

Even though the UK's overarching treatment for depression and anxiety is antidepressant prescribing, the DSM-IV-TR (2000) advocates with holding a diagnosis of mania or bipolar if a person has been taking psychiatric drugs which induced iatrogenic neuropsychiatric problems. Additionally, this situation needs to apply to all general medications and street drugs before an affective or SMI diagnosis is made. Page 191 of the DSM-IV-TR states, "resolution of symptoms can take weeks or months and may require treatment" which potentially means treatment with neuroleptic drugs.

For susceptible populations who have certain 5-HTT polymorphisms and are PMs, IMs, or UMs for prodrugs, further drug treatment requiring the same metabolic pathways, is likely to incur and further neuro-psychiatric chemical reactions including violence.

Homeostasis

Homeostasis is maintained in the brain by interactions mediated by continually changing neurotransmitters, responding to toxins from outside of the body. This constant compensatory change is essential for survival in the face of changing physical and psychological external environments.

Neurotransmitters are interdependent, a disturbance in one results in an imbalance in all. Out of the innumerate neurotransmitters identified, the functions of which are still being researched, it is known that dopamine inhibitor and serotonin enhancer drugs or medications lead to the disruption of homeostasis, due to the reciprocal interaction between the dopaminergic and serotonergic systems.[168]

When serotonergic and/or dopaminergic drugs cross the blood brain barrier, an unknown number of up to a thousand neurotransmitters respond. If a few days later, for example, in the case of psychiatric drugs, the dose is changed, or another drug is added, neurotransmitters respond to the challenge. After about 36 hours, or however long the substance takes to cross the blood brain barrier, neurotransmitters respond again because relative levels of neurotransmitters are being disturbed. Changes at brain levels can occur during the course of a single day in UMs and with PMs and IMs the concentration of toxins increases over time.

During this period of iatrogenic chemical disruption of homeostasis, the person has involuntary, unpredictable changes in emotional and cognitive function. Often suicidality recedes to be replaced with cognitive and emotional impairment and sometimes these effects are long lasting, even permanent. Chronic and tardive neurotoxicity, with or without akathisia, supervenes and may continue in the absence of psychiatric drugs that caused the initial neurotoxic reaction.

Serotonergic drugs include atypical and typical neuroleptics and MAOIs, TCAs, SSRIs and SNRIs and certain general medications.

Dopaminergic and serotonergic psychiatric drugs and general medications are linked with akathisia/agitation; the possibility of violence to the person themselves or others is due to the many neuropsychiatric behavioural reactions.[3,173]

A life threatening ADR from serotonergic drugs is Serotonin Syndrome (SS), previously called serotonin toxicity, due to excessive serotonergic activity, [174,175] with 40% of persons experiencing iatrogenic neuropsychiatric reactions.[176]

All neuroleptics have anticholinergic properties which disrupt the dopamine-acetylcholine equilibrium.[179, 180] In response the body compensates, creating a rebound effect by

Table 8. General medications associated with serotonin syndrome[169-172]

Drug Type	Name
Analgesics	Cyclobenzaprine fentanyl pethidine tramadol pentazocine methadone buprenorphine
Antitussives	dextromethorpham
Antibiotics	linezolid
Antiviral	ritonavir
Migraine medications	almotriptan amerge axert carbamazapine eletriptan frovatriptan imitrex naratriptan sumatriptan rizatriptan zolmitriptan
Antiemetics	dropericdol granisetron metoclopramide ondansetron
Antiobesity Agent	sibutramine
Parkinson's Disease	selegilene
Muscle Relaxants	flexaril metaxalone
Miscellaneous	methylene blue

Table 9. Serotonin syndrome-neuropsychiatric ADRs[16,176-178]

Agitation	delirium	hyperactivity
Aggression	disorientation	hypomania
Akathisia	drowsiness	irritability
Anxiety	excitement	restlessness
Confusion	hallucinations	suicidality

producing and releasing more acetylcholine, which causes autonomic instability.[181] "This adaptation replicates the effect of organophosphate poisoning (whether by nerve gas, by insecticide, or by anti-Alz heimer's pharmaceuticals) by ***over stimulating acetylcholine circuits of the brain.***" [181]

Behavioural reactions associated with NMS, which can occur with certain general medications, SSRIs, SNRIs,[182] and neuroleptics, include confusion, violence, paranoia, delusions, aggression and agitation.[183]

The overlapping features of autonomic instability of NMS and OP include the toxic behavioural reactions of aggression, agitation and violence. It needs to be recalled that phenothiazine, prior to being developed into the phenothiazine group of major tranquillisers, (chlorpromazine, trifluperazine and fluphenazine), was used initially as an insecticide in 1934.[184]

Table 10. The symptom similarities of NMS and Organophosphate Poisoning (OP).[181,183]

Neuroleptic Malignant Syndrome	Organophosphate Poisoning
autonomic nervous system disturbance	autonomic
aggression, agitation and violence	*Aggression*
confusion	*dementia, psychosis, anxiety, depression, tremors*
Muscle rigidity	paralysis, dystonia, cranial nerve palsy and polyneuropathy
Coma, alterations of consciousness	loss of consciousness
Muscle breakdown	weak respiratory and limb muscles
Fever	Seizures

DISCUSSION

Mental health sectioning is frequently used when patients become physically aggressive. Aggression and violence is common- place with some patients who are treated with antidepressant and neuroleptic psychiatric drugs. Treatment emergent violence resulting from antidepressants, neuroleptics and serotonergic/dopaminergic medications, covers a wide range of neuropsychiatric behavioural changes, some of which are fatal, whilst others necessitate hospital admission.

Two decades ago, hospital admission rates for antidepressant induced psychosis or mania in a fourteen-month period was notable at 8.1%.[56] The UK hospital admissions for psychiatric iatrogenic conditions can only be surmised, as these statistics are not recorded. Nonetheless, in the last decade, the rising numbers of people accessing NHS MH services, the rise of antidepressant prescribing [164] and 'the use of section 136 of the Act (where people are brought to a 'place of safety') increased by 18%' from 2015-2016[155] provide some indication towards UK's emergency hospital admissions caused by iatrogenic psychiatric drug psychosis and mania.

Over the years clinicians have believed psychiatric drugs are essential in helping people with emotional distress. This indoctrination is so ingrained that the concept of psychiatric treatment inducing violence is inconceivable to prescribers and policy makers, who abide by conventional drug treatment. The common factor of aggression in organophosphate poisoning and NMS is striking.[181,183] Although aggression is a known symptom of OP poisoning, acetylcholine disruption stemming from neuroleptics is not acknowledged as an iatrogenic cause of violence in SMI.

People experiencing iatrogenic behavioural changes from psychiatric drugs and general medications are incredibly vulnerable, as the vast majority of clinicians in the UK neither recognise nor consider that genetic variations influence the outcome of drug prescribing. Prescribers do not know the SmPC standard dosage specifically applies to EMs, as PMs are excluded from phase II onward in clinical trials.[185,186,187] Athough this yardstick dosage is safe for EMs, the dosage is unsafe for PMs, IMs and UMs of pro- drugs. Genetic variations in 5-HTTLPR and 5-HTT also determine the therapeutic efficacy or ADRs to serotonergic drugs. [114,145] Persons with genetic variations require adjusted dosage to avoid being subjected to undesirable behavioural ADRs. People suffering from akathisia are prone to respond violently to perceived insult, provocation or "psychological blow" being unable to cope with disrespectful attitudes from others. Even though new drugs are required to state the different drug dosage for different rates of metabolism[188] the older drugs will continue to be prescribed at the standard dose thereby perpetuating insufferable iatrogenic behavioural reactions for everyone with genetic variations.

Clinicians who fail to adhere to the DSM criteria for a MH diagnosis,[81] inaccurately deduce that iatrogenic serotonergic and dopaminergic behavioural reactions are functional as opposed to the true nature of the toxic organic condition. The outcome results in a social construct with persons acquiring a mental health diagnosis. Iatrogenic psychosis or mania is a benchmark for an SMI diagnosis, which precedes enforced legal treatment with traditional neuroleptics. Although it is considered legally acceptable, the fact that PMs, IMs and UMs of prodrugs who, due to their sub-optimal metabolism,[148] experience psychological degeneration with involuntary violent reactions, is reprehensible. Additionally, whether the MH condition is organic or functional, for people with CYP450, 5-HTTLPR and 5-HTT polymorphisms, subsequent neuroleptic treatment involving similar metabolic pathways to antidepressants, is not therapeutic. Since many neuroleptics have serotoninergic activity, 5-HTT and 5-HTTLPR testing would benefit patients prior to neuroleptic prescribing, as well as CYP450 genotype screening.

Research studies have identified antidepressants and specific genetic variations are linked with the following behavioural ADRs: akathisia, agitation, restlessness, insomnia, suicide and homicide ideation, psychosis, delusions, hallucinations, mania, suicide and homicide.[46,111-117]

The RCPsych in declaring these research studies are insufficient to advocate clinical retrospective genotyping is improvident and short-sighted. The scale of the research size is immaterial and does not invalidate outcomes.

The primary reason for prescribers' naivety about neuropsychiatric behavioural ADRs and inefficient metabolism, is due to pharmaceutical companies' omission to state drug dosage for the different rates of metabolism. Secondly, suppression of genotyping from both doctors and the public is compounded by many UK acclaimed public health bodies by various attitudes; genotyping is outside their remit, responsibility is shunted elsewhere, or they are waiting for further psychiatric drug research behavioural outcomes. Waiting could go on ad finitum as current UK psychiatric drug research is concerned only with psychiatric drug physical ADRs; behavioural ADRs in relation with different rates of metabolism are not being addressed by research. Although £20 million is allocated to MH research for the next 5 years,[189] unless pharmacogenetics, genotype status and toxic behavioural ADRs are made visible to both public and doctors, the chances of future research is unpromising.

In 2011, the European Medicines Agency (EMA), responsible for authorising drugs in Europe, took a degree of responsibility towards patient safety. Guidelines were issued to pharmaceutical companies with the aim of making drugs safer in relation to drug development, pharmacogenetic testing and dosage for specific genetic populations.[187] However despite the EMA's recent 2017 concept paper [188] explaining metabolic terminology, in order to 'contribute to optimizing efficacy and preventing adverse drug reactions', this guideline applies to new drugs only. Meanwhile all older psychiatric drugs are still being prescribed at the standard dosage with persons who have genetic variations or polymorphisms still being exposed to disastrous neurotoxic behavioural ADRs, including akathisia which precedes violence and suicide. The international Clinical Pharmacogenetics Implementation Consortium is the sole corporate body that shows accountability for persons safety when antidepressants are prescribed, by providing guidelines for TCA and SSRI dosage in relation with CYPC19 and CYP2D6 polymorphisms.[190,191]

With the increasing use of neuroleptic,[163] antidepressant[161] and general medications, we hypothesise violent behaviour will escalate amongst people with a 'mental health condition' as well as those without a history of a 'mental health condition', either in the community, acute wards, secure units, prisons or outpatient units. Because of the higher frequency of lower metabolism at CYP450 2D6 in African Americans compared to Caucasians,[150] the rates of detention for the 'Black or Black British' group which are currently over four times those of the White group[192] will rise at the same rate.

Increased admissions to the UK's PICUs, Mental Health Act detentions and Community Treatment Orders are envisaged. Apart from expensive hospital care, other costs in association with extended treatment, are likely to include UK's Personal Independence Payment, Employment Support Allowance and Self Directed Support; lifelong costs which are likely to follow on from protracted treatment costs. These factors together with the cost to the economy as a consequence of lost productivity, currently at £70-100 billion annually, [189] will accelerate. Statistically, the numbers of people who have been physically and psychologically disabled by psychiatric drugs that were supposed to have helped them is unknown; neither are there figures available in the UK for people who were prescribed psychiatric drugs and subsequently committed homicide.

In order to reduce the MH financial burden and to minimise treatment emergent violence due to trial and error prescribing, clinicians' pharmacogenetic knowledge needs to be heightened in all aspects of health and social care, together with knowledge of the different presentations of akathisia[14] in the role of violence. It is essential for undergraduates at British Medical Schools to have an understanding of genotyping,[148] thereby fostering an appreciation of how ADRs arise. Retrospective genotyping reduces financial costs for inappropriate psychiatric drugs and subsequent healthcare costs [193] and even though genotype testing incurs a one off cost, the results last a lifetime, reduce treatment failure and subsequent toxic episodes.[194] Genotyping guides safe clinical practice in the prescription of antidepressants and neuroleptics as well as serotonergic and dopaminergic general medications. [143]

The GMCs states 'Our statutory purpose is to protect, promote and maintain the health and safety of the public by ensuring proper standards in the practice of medicine.' Other acclaimed UK public heath bodies emulate similar aspirations. Nevertheless, none of these public bodies are willing to put their head above the parapet to promote a life saving genotyping test. Lackadaisical attitudes negating the integration of retrospective genotype testing and remaining on the sidelines needs to change, as turning a blind eye has already endangered current MH patients let alone lives of future MH patients, and will not improve MH outcomes. The adoption of routine genotyping in the NHS prior to prescribing psychiatric drugs, and the implementation of the antidepressant CPIC guidance into clinical practice would indicate UK policy makers are showing accountability and responsibility in supporting prescribers towards increased patient safety.

CONCLUSION

Serotonergic and/or dopaminergic psychiatric drugs and general medications can cause neurotoxic akathisia, which precedes treatment emergent violence. Akathisia, suicidal and homicidal behavioural reactions are undisputedly linked with antidepressants and specific genetic variations. Pharmacogenetic education is essential to increase clinicians understanding of how inter-individual different genetic status directly affects psychiatric drug therapeutic outcome, how neurotoxic behavioural ADRs arise and the reason for

antidepressant 'treatment failure'. Genotype screening would contribute significantly in reducing treatment emergent violence and dependence upon the mental health and welfare benefits system. In order to eliminate one-size-fits-all precarious prescribing, for the safety and well being of patients, professionals and the public, retrospective genotyping is paramount.

EPILOGUE

There are few who will see the analogy between Simon and Garfunkel's 'The Sound of Silence' and present day clinical practice. People talking without speaking, people hearing without listening. For silence, like a cancer, grows and if clinicians continue to bow and pray to the neon god of psychiatric drugs, the neon warning lights will continue to flash ad infinitum with silent raindrops, falling like tears, echoing in the wells of silence within the institution tenement halls of forgotten people, damaged by psychiatric drug toxicities.

And no one dared disturb the sound of silence.

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