

Treatment Emergent Violence to Self and Others: A Literature Review of Neuropsychiatric Adverse Reactions

Catherine Clarke SRN, SCM, MSSCH, MBChA., Jan Evans MCSP. Grad Dip Phys.,
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Abstract -*This paper reviews the literature linking physical violence, directed towards self or others, to psychiatric 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 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 – *Drugs that target the brain have effects that are not always the ones intended. How individuals react to drugs and drug-drug combinations is governed by their genetic makeup. Phase 1 of drug metabolism is the polymorphic CYP450 system dividing the population into poor, extensive (normal), intermediate and ultra rapid metabolisers, at one or more of three enzyme producing genes CYP450 2D6, 2C9 and 2C19. Variations in the serotonin transporter gene (5-HTTLPR) and serotonin receptors (5-HT) influence the outcome of serotonergic medications. It is established that genetic polymorphisms in the CYP450 and serotonergic metabolising system cause higher medication blood levels which are associated with neuropsychiatric adverse drug reactions, 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 medications.*

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 modern general medications and antipsychotics with neuropsychiatric behavioural reactions is notable. There is limited information about homeostasis and the disruption of neurotransmitters linking violence with antidepressants and antipsychotics. These issues indicate further research and pharmaceutical transparency about the role of CYP450, 5-HTTLPR and 5-HT polymorphism associated neuropsychiatric reactions for all psychiatric and modern general medications.*

Practical implications – *Safer prescribing is important and could be achieved by individual genotyping test, which would highlight susceptible persons with genetic polymorphisms. Prevention of violence would enhance patient, ground floor practitioner and public safety.*

Originality/value - *This paper is the first review that implicates certain as a cause of violence due to pharmacogenic polymorphisms and neurotransmitter disruption.*

Keywords - *Violence, suicide, homicide, psychosis, akathisia, medication, antidepressant, antipsychotic, pharmacogenetics, CYP450, neurotransmitter*

Paper type - *Review*

Introduction

There is continuing controversy about patients and violence; a critical appraisal of the available evidence is presented. Suicide, (violence towards self) and homicide, (violence towards others) can be triggered by patients experiencing aggression and violence, a feature of akathisia caused by psychiatric medications.

Antidepressants are prescribed for common mental health disorder such as depression or anxiety and although some of these patients respond well to treatment others commit violence even though there was no violent history prior to taking treatment.

Similarly patients diagnosed with severe mental illness (SMI), schizophrenia or bipolar are treated with antipsychotic medication. Although violence is known when alcohol and/or recreational drugs are used in conjunction with antipsychotics, some patients prior to SMI diagnosis have no history of violence, neither have they used alcohol or recreational drugs during psychiatric treatment. Violent incidents may be committed *after* being diagnosed and treated for SMI.

Before 1986 and the advent of new generation antidepressants and antipsychotics, people diagnosed with depression and schizophrenia were treated with older antidepressants and older typical antipsychotics. Following promotion of new generation antidepressants some treated patients became suicidal and others developed mania, hallucinations and delusions. Some 40% of the population have pharmacogenetic CYP450 polymorphisms, impeding efficient metabolism of some general and psychiatric medications. Together with the concurrent disruption of neurotransmitters and homeostasis induces behavioural changes. Thus populations with pharmacogenetic CYP450 polymorphisms prescribed a general medication can incur diagnosis with a common mental health disorder which, when treated with psychiatric medications, can induce violence leading to a SMI diagnosis.

Akathisia

Drugs used in psychiatry and some general medications cause akathisia, which is an extrapyramidal side effect (EPSE), a neuropsychiatric behavioural reaction. Originally described in 1901 by neuropsychiatrist Ladislav Haskovec,^{1 Brune & Sachdev} akathisia was initially associated with hysteria.^{2 Mohr} Nervous disorders in asylums were treated extensively with potassium bromide that caused tremor side effects and were likely to be the true nature of akathisia.

Akathisia was formally recognised in the late 1950's to 1970's^{3 Hodge, 4 Raskin} and is related to high medication doses, rapid increases or changes in dose^{5 Lane, 6 Bratti} either up or down. The response to alterations in medication blood levels and toxic levels of medication causes neuropsychiatric behavioural disturbances which are idiosyncratic and stem from genetics. The symptoms of akathisia include dysphoria,^{5 Lane, 7 Loonen} 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.'^{8 Schulte} Alternative

clinical diagnosis may include anxiety, depression, agitation, exacerbation of psychosis or other psychiatric causes.^{9 Sachdev}

‘The state causes heightened irritability and frustration with aggression against self or others, and often a generally worsening of the mental condition.’^{10 Breggin}

Hallucinations, psychosis, depersonalization, abnormal thinking and delirium are symptoms which sometimes result from a superimposed toxic state,^{10 Breggin} i.e. a toxic psychosis.

When experiencing akathisia, a patient is prone to respond violently to perceived insult, provocation or “psychological blow” being less able to cope with disrespectful attitudes from others.

Medications used in psychiatry

Antipsychotics:

In the 1950’s, stelazine, haloperidol and chlorpromazine were classified as major tranquillizers and used for acute anxiety and schizophrenia; the term antipsychotic was introduced by drug companies as a marketing ploy. Neuroleptic is a more accurate term and was 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 which had already been identified.’^{11 Jackson p.155} Because of common usage, the term antipsychotic is used throughout this document, as opposed to neuroleptic.

The rates of akathisia increased with typical antipsychotics (major tranquillisers)^{2 Mohr} and were thought to decrease with the new generation atypical antipsychotics that were promoted as causing less EPSEs. However, akathisia rates remained high, up to 39%, after their introduction in the late 80s.^{12 Zyprexa, 13 Kumar, 14 Sachdev, 15 Sachdev} Acute akathisia tends to persist for as long as neuroleptic medications are continued, although the intensity may fluctuate over time. The reported prevalence of akathisia among individuals receiving neuroleptic medication has varied widely (20%-75%);^{16 Miller} 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.

Older antipsychotics’ acute akathisia rates range from 8% to 76% and less is claimed for new generation atypical antipsychotics.^{7 Loonen} Consequently, this factor is associated with overlooking the diagnosis of akathisia with atypical antipsychotics.^{17 Hirose}

Table 1: Akathisia related toxic behavioural symptoms: typical antipsychotics

TYPICAL ANTIPSYCHOTICS	NEUROPSYCHIATRIC REACTIONS
clopixol	agitation, akathisia
haloperidol	restlessness, agitation, akathisia
trifluoperazine	restlessness
sulpiride	restlessness, akathisia

⁸ Schulte, ¹⁸ Herrera, ¹⁹ NICE, ²⁰ SmPCs

Table 2: Akathisia related toxic behavioural symptoms: atypical antipsychotics

ATYPICAL ANTIPSYCHOTICS	NEUROPSYCHIATRIC REACTIONS
Aripiprazole	restlessness, agitation, akathisia
Amisulpride	agitation
Clozaril	akathisia, agitation, aggression, disruptive behaviour
Olanzapine	restlessness, agitation
paliperidone/invega	akathisia, aggression
Quetiapine	akathisia, irritability
Risperidone	agitation
Sertindole	akathisia
Zotepine	akathisia

¹⁹ NICE, ²⁰ SmPCs, ²¹ Mansour

Akathisia was found to be the predisposing factor in 50% of violent incidents during antipsychotic treatment.²² Crowner Both typical and atypical antipsychotics are associated with violence,¹⁸ Herrera, ²³ Swanson suicidal and homicidal behaviour, ²⁴ Van Putten suicide,²⁵ Healy, ⁸ Schulte and homicide.⁸ Schulte 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.⁸ Schulte

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 1924.²⁵ Healy, ²⁶ Lawrence, ²⁷ Saha, ²⁸ Burgess, ²⁹ Colton People with schizophrenia have higher rates of suicide compared with the general population,²⁷ Saha with a 4 to 6 fold increased risk of violent behaviour.³⁰ Fazel In placebo-controlled trials excess suicides in psychosis are linked solely with antipsychotics.³¹ Healy

Antidepressants:

When the new generation antidepressants were introduced in the mid 1990s, akathisia became even more prominent.⁵ Lane, ⁷ Loonen, ³² Koliscak Akathisia is a listed side effect of the new generation Selective Serotonin Reuptake Inhibitor (SSRI) and Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) serotonergic antidepressants.⁷

The DSM-IV-TR states akathisia can be associated with dysphoria, irritability, aggression or suicide attempts, behavioural dyscontrol,³⁵ DSM-IV-TR severe anxiety, peculiar bodily sensations, bizarre thinking and reasoning.³⁶ Fouks Antidepressant induced akathisia worsens mental stability, being connected with violence,³³ Healy, ³⁷ Moore suicide ideation,³⁸ Hansen, ³⁹ Tueth, ⁴⁰ Wirshing, ⁴¹ Effexor suicide attempt,⁴² Rothschild, ⁴³ Healy homicidal ideation⁴¹ Effexor and homicide.⁴⁴ Lucire 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.⁴⁵ Genmullen 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.³³ Healy

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.’⁴⁶ Healy 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.’

¹¹ Jackson p. 72

Other neuropsychiatric reactions connected with antidepressant medications: venlafaxine, marketed as an SNRI, can cause hysteria, impulse control difficulties, paranoid reaction, psychotic depression,⁴¹ Effexor mania/euphoria, hallucinations, aggression and delirium.⁴⁷ eMC SSRI paroxetine,⁴⁸ FDA citalopram⁴⁹ Beckwith fluvoxamine⁵⁰ Breggin and sertraline⁵¹ Mendhekar and SNRI duloxetine⁵² Peritogiannis are linked with mania. Paroxetine can also induce hallucinations.⁴⁸ FDA 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 withheld from the public by Eli Lilly since 1984. When no mania or psychosis is in evidence before medication, it becomes clear these neuropsychiatric reactions are iatrogenic.

In antidepressant clinical trials, akathisia has been miscoded as, "agitation, emotional lability and hyperkinesia (over activity)"³³ Healy 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.⁵³ Breggin Recently COSTART has been replaced by MedDRA, 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 symptoms are a precursor to either worsening of depression or the emergence of suicidal impulses, there is concern that patients who experience one or more of these symptoms may be increased risk for worsening depression or suicidality. In these circumstances therapy should be evaluated, and medications may need to be discontinued when symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Some people taking psychiatric drugs develop akathisia and some people who develop akathisia kill themselves or others. Yet the drugs can be effective in persons suffering serious and severe depression, provided their doses are adjusted according to their ability to metabolise them normally and there is informed monitoring.⁴⁴ Lucire

Dysphoria may or not be associated with akathisia⁵⁴ King and is defined as an "...extremely unpleasant and distressing subjective change in mood."⁵⁵ Thomas

Dysphoria has been linked with a high rates of suicide in the first year of antipsychotic treatment³¹ Healy and needs to be recognised in order to prevent a worsening state of mental health.

Whether new generation antidepressants are prescribed for other common mental health conditions i.e. generalised anxiety, panic, post traumatic stress and obsessive compulsive disorders and social phobia⁵⁶ IAPT or health conditions where there is no

history of mental illness, such as smoking cessation or premenstrual dysphoric disorder,^{33 Healy} some people will experience akathisia, violence and suicidal or homicidal neuropsychiatric reactions. Because akathisia is under diagnosed^{17 Hirose} and often misconstrued as an ‘uncovered’ mental illness or an intractable mental illness,^{57 Van Putten} it’s recognition is essential to safe guard against worsening mental stability.

Withdrawal from Psychiatric Drugs

Withdrawal from psychiatric drugs can cause neuropsychiatric behavioural reactions. For example, benzodiazepine withdrawal can cause anxiety and confusion; lorazepam and oxazepam, with a shorter ½ life, carry risk of toxic psychosis, or a condition resembling delirium tremens on withdrawal.^{58 BNF} MIND, mental health charity, reports antipsychotic withdrawal can cause restlessness, irritability and agitation, which are akathisia symptoms. Akathisia is associated with SNRI withdrawal.^{59 Shelton} SSRI withdrawal effects include irritability,^{60 Coupland, 61 Perahia, 62 Schatzberg} agitation,^{62 Schatzberg} EPSE,^{63 Vlaminc} akathisia,^{59 Shelton, 64 Wolf} aggression^{50 Breggin} and risk of suicidality.^{33 Healy} Withdrawal psychosis is linked with prozac treatment.^{45 Genmullen} The older generation monoamine oxidase inhibitor and tricyclic antidepressant withdrawal symptoms include EPSE,^{63 Vlaminc} akathisia,^{59 Shelton} and hypomania/mania.^{65 Naryan, 66 Dilsaver}

Withdrawal effects may be mistaken for a relapse.^{67 Lejoyeux} Although relapse predictors rate levels of akathisia and EPSE,^{68 Robinson} these symptoms need to be recognised as neuropsychiatric behavioural reactions as opposed to a state of mental illness. Being fully aware of patients’ perpetual internal agitation and heightened irritability, and having respectful behaviour and attitudes in relationship with patients is paramount to prevent verbal and physical aggression.

Medications used in General Practice

Many general medications can cause psychiatric effects.^{69 Ashton} Anaesthetic drugs, acne, indigestion, hypertension, angina, asthma, antismoking, antibiotics and antimalarial medications may cause akathisia, depression, suicide ideation and psychosis.

Drugs as diverse in structure and function as:

- hypericum (St John’s wort)
- varenicline (Chantix®; Pfizer, New York, NY)
- oseltamivir (Tamiflu®; Genentech USA, Inc, San Francisco, CA)
- isotretinoin (Roaccutane®; Hoffman-La Roche, Basel, Switzerland)
- mefloquine (Lariam®; Hoffman-La Roche)
- metoclopramide (Maxolon®; Shire plc, St Helier, Jersey, UK; Reglan®; UCB, Brussels, Belgium)
- zolpidem (Stilnox®; Sanofi-Aventis, Paris, France)
- calcium channel blockers
- antiepileptic drugs mooted as “mood stabilizers”
- reserpine
- benzodiazepines
- statins
- interferon^{44 Lucire}

All can induce suicidal and homicidal thinking as an occasional side effect. Moore et al (2010) identified 1527 cases of violence, including homicides, disproportionately reported to the FDA for 31 drugs, including varenicline, eleven antidepressants, six

sedative/hypnotics and three drugs for attention deficit hyperactivity disorder. ^{37 Moore, 44 Lucire}

Table 3: General medications associated with toxic neuropsychiatric reactions.

DRUG CLASS	NAME	NEUROPSYCHIATRIC REACTIONS
Anti-histamine	non sedating: loratidine..... rupatadine..... desloratidine..... sedating: promethiazine..... chlorphenamine..... cyproheptadin.....	*EPSE, depression, sleep disturbances, tremor *see loratidine effects; irritability *see loratidine effects; hallucinations ^{58 BNF} *EPSE, depression, insomnia, tremor, akathisia, Neuroleptic Malignant Syndrome (NMS), agitation, excitement, insomnia ^{58 BNF} *see promethiazine effects *see promethiazine effects ^{58 BNF}
Anti-emetic	prochlorperazine..... droperidol..... domperidone..... metoclopramide.....	*akathisia, EPSE, tremor, NMS, agitation, excitement, insomnia ^{58 BNF} *see prochlorperazine effects; anxiety, hallucinations ^{58 BNF} *see prochlorperazine effects; anxiety, nervousness ^{58 BNF} *see prochlorperazine effects; suicide attempt ^{70 Chow}
Anaesthetic	triflupromazine	extreme akathisia ^{71 Krause}
Benzodiazepine	midazolam..... diazepam, lorazepam and alprazolam.....	hallucinations, paradoxical excitement and aggression ^{58 BNF} aggression, hostility, anxiety, talkativeness and excitement, aggressive and antisocial acts. ^{58 BNF}
Cold remedies	pseudoephedrine..... (sudafed)	anxiety, restlessness, hallucinations ^{58 BNF}
Antibiotics	quinolones..... levofloxacin..... nalidixic acid..... cephalosporins..... carbapenems: ertapenem..... metronidazole.....	*restlessness, ^{72 BNF 2006} anxiety, depression, hallucinations, tremor, psychoses ^{58 BNF} *see quinolone effects; abnormal dreams, EPSE *see quinolone effects; toxic psychosis ^{58 BNF} hyperactivity, nervousness, sleep disturbances, hallucinations ^{58 BNF} anxiety, depression, agitation, tremor, hallucinations ^{58 BNF} psychotic disorders ^{58 BNF}
Anti-fungals	voriconazole..... griseofulvin.....	anxiety, depression, agitation, insomnia, hallucinations, tremor, ^{58 BNF} sleep disturbances, agitation, depression ^{58 BNF}
Anti-malarial	mefloquine..... chloroquine..... proguanil..... with atovaquone (malarone)	tremor, abnormal dreams, insomnia, acute anxiety, restlessness, depression, psychosis, suicidal ideation, suicide ^{58 BNF} ESPS ^{58 BNF} abnormal dreams, depression, anxiety, hallucinations ^{58 BNF}

DRUG CLASS	NAME	NEUROPSYCHIATRIC REACTIONS
Anti-parkinson	monoamine-oxidase-B inhibitors: selegilene..... levodopa: madopar..... dopamine agonists: pergolide..... (ergot) pramipexole..... (non-ergot)	depression, psychosis, tremor, movement disorders, sleeping disorders, agitation, anxiety ^{58 BNF} EPSE, psychosis, euphoria, abnormal dreams, insomnia, depression, suicidal ideation, anxiety, agitation, NMS, compulsive behaviour ^{58 BNF} hallucinations, compulsive behaviour, impulse control disorder (ICD)** hyperkinesia, hallucinations, restlessness, compulsive behaviour, ICD**, delusion, paranoia ^{BNF}
Anti-smoking	varenicline bupropion.....	sleep disorders, abnormal dreams, depression, anxiety, hallucinations, panic attack, mood swings, tremor, restlessness, aggression, irrational behaviour, psychosis, suicidal ideation, sleep-walking, agitation ^{58 BNF} agitation, anxiety, depression, insomnia, tremor, abnormal dreams, hallucinations, hostility, irritability, aggression, delusions, paranoid ideation, restlessness, suicidal ideation ^{58 BNF}
Acne medication	isotretinoin: acutane..... roaccutane..... azithromycin..... clarithromycin..... telithromycin.....	depression, psychosis, and suicide ^{73 O'Donnell} depression, aggressive behaviour, anxiety, psychosis and suicidal ideation ^{58 BNF} anxiety, sleep disturbances, agitation insomnia, nightmares, anxiety, psychosis insomnia, nervousness, hallucinations ^{58 BNF}
Angina and Hypertension	calcium channel blockers..... beta blockers..... peripheral vasodilators..... ACE inhibitors..... ranolazine.....	sleep disturbances, mood changes, tremor, EPSE, anxiety, depression ^{58 BNF} sleep disturbances with nightmares, psychoses, depression ^{58 BNF} insomnia, abnormal dreams, anxiety, agitation, sleep disturbances ^{58 BNF} sleep disorder, dream abnormalities, insomnia, nervousness, depression, anxiety, mood changes, tremor ^{58 BNF} tremor, anxiety, hallucinations ^{58 BNF}
Hypnotics	zaleplon..... zolpidem..... zopiclone..... clometiazole.....	*depression, hallucinations, hostility, aggression, sleep-walking ^{58 BNF} *see zaleplon effects; agitation, nightmares ^{58 BNF} *see zaleplon effects; nightmares ^{58 BNF} paradoxical excitement ^{58 BNF}

DRUG CLASS	NAME	NEUROPSYCHIATRIC REACTIONS
Indigestion and Acid Reflux	proton pump inhibitors: (PPIs) omeprazole..... lansoprazole..... H ₂ antagonists..... imetidine/tagamet ranitidine/zantac	*sleep disturbances, depression, hallucinations ^{58 BNF} *see PPI effects; irritability, ^{74 Qinhui} agitation, ^{58 BNF} aggressive behaviour ^{75 NHS Choices} *see PPI effects; restlessness, tremor ^{58 BNF} psychiatric reactions: depression, hallucinations, involuntary movement disorders ^{58 BNF}
Corticosteroids	glucocorticoid..... betamethasone dexamethasone hydrocortisone prednisolone	euphoria, nightmares, insomnia, irritability, mood lability, suicidal thoughts, serious paranoid state or depression with risk of suicide, corticosteroid-induced psychosis ^{58 BNF}
Inhaled Corticosteroids	used in asthma and COPD (chronic obstructive pulmonary disease)	anxiety, depression, sleep disturbances, behavioural changes including hyperactivity, irritability, aggression (particularly in children) ^{58 BNF}
Opioid Analgesics	tramadol..... buprenorphine.....	*hallucinations, euphoria, dysphoria, mood changes, depression, sleep disturbances ^{58 BNF} *see tramadol effects; agitation, anxiety, restlessness, tremor, psychosis ^{58 BNF}
Cholesterol lowering drugs	statins..... simvastatin..... atorvastatin..... mevastatin.....	*sleep disturbance, depression ^{58 BNF} aggressive or violent behaviour ^{76 Golomb} *see statins effects *see statins effects *see statins effects; anxiety ^{77 Shrivastava}

**Treatment with dopamine-receptor agonists and levodopa is associated with impulse control disorders, (ICD), ^{58 BNF} characterized by “problems in emotional and behavioral self-control” ^{78 DSM-V} and failure to resist a temptation, urge or impulse that may harm oneself or others.

Table 3 is not inclusive of all the general medications which cause toxic neuropsychiatric reactions. In brief any drug that has akathisia, also miscoded as agitation, emotional lability and hyperkinesia, among its side effects is 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 drugs may lead to a mental health diagnosis from the unwary clinician. In the presence of substance 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.’ ^{79 DSM-IV-TR} 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.

Table 5: Outline of the differences between mental states due to toxicity and functional psychoses

MENTAL STATES DUE TO TOXICITY	THE FUNCTIONAL PSYCHOSES
Toxin or medication in use or recently used.	All “functional psychoses” carry the exclusion, “not caused by substance or medication”
<p>Akathisia, restlessness, obsessive preoccupation with death, dying and suicide.</p> <p>Inexplicable impulse to kill people one most loves, violence, behavioural dyscontrol, confusion/ambulant delirium, manic shift.</p> <p>Confusion misidentification</p> <p>Weird violent dreams, insomnia</p> <p>Hallucinations</p> <p>Sick, vomiting, tachycardia, loss of coordination, cognitive impairment and memory problems.</p> <p>Confabulations, shifting false reports, misinterpretation, serotonin toxicity or neuroleptic malignant syndrome.</p>	<p>Clear mind</p> <p>Absent: confusion.</p> <p>Absent: physical / neurological disease. Absent: substance/medication use.</p> <p>Absent: causation.</p> <p>Specific voice hallucinations, rare if ever visual</p> <p>Fixed delusions, correctly defined.</p> <p>Mania or depression.</p>
Prominent: confusion, lack of coordination memory/cognition impaired.	Absent: confusion, lack of coordination, otherwise clear thinking.

Ref: Dr. Yolande Lucire, personal communication 26th Feb 2014.

Toxic behavioural reactions that can occur with cannabis are hallucinations, paranoia^{80 RCP} psychosis^{81 Henquet} and the akathisia symptoms of irritability and aggression.^{80 RCP} Violence,^{82 Moore} homicide^{83 US Dept. of Justice, 84 Los Angeles Times} and suicide^{85 Price} are reported from cannabis use. Methamphetamine and cocaine, may also be associated with paranoid reactions and violence.^{10 Breggin}

The magnitude of the problem

The connection between violence and people diagnosed with a mental disorder has been verified by many studies.^{86 Brennan, 87 Swanson} Suicide associated with medication began to emerge in the 1950s, when typical antipsychotics, associated with a high rate of akathisia, such as fluphenazine^{88 Shear} and haloperidol^{8 Schulte} were introduced. From late 1980s violence and suicide tended to rise again^{25 Healy, 27 Saha, 89 Joukamaa} which coincided with the introduction of new generation antidepressants associated with iatrogenic akathisia.

In a recent study of 1,829 New Zealanders taking antidepressants, 39% experienced suicidality.^{90 Read} 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.^{91 Larsson}

The number of suicides among UK mental health patients climbed to 1,333 in 2011, an increase of 158 more suicides than in 2010. During 2001-2011, in the UK, 10% of people convicted of homicide were identified as patients, i.e. the person had

been in contact with mental health services in the 12 months prior to the offence and 6% were psychotic at the time of the offence, an average of 33 per year.^{92 Manchester Uni.} The common denominator for these violent incidents is the likelihood patients were treated with new generation antidepressants or antipsychotics which incurred akathisia neurotoxic reactions.

Admission to Psychiatric Intensive Care Units (PICU) is commonly due to aggressive behaviour^{93 Bowers} and in three acute psychiatric units in Australia, 58% of all incidents were violent with agitation preceding incidents.^{94 Owen} Aggression rates almost tripled with some prison inmates who were prescribed antipsychotics to control aggression.^{95 Workman} 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.*^{96 NICE} This guideline addresses many issues, however, it does not address akathisia and the role of pharmacogenetics in CYP450 metabolism for psychiatric/general medications, cannabis and other recreational drugs, nor iatrogenic neurotransmitter disruption.

Pharmacogenetics

Many medications are broken down or metabolised by the genetically diverse Cytochrome CYP450 enzymes, which is the first stage of metabolism. “Antidepressants, antipsychotics, antiarrhythmics, antiemetics, beta-adrenoceptor antagonists (beta-blockers) and opioids” are metabolised by CYP450 2D6,^{97 Zhou} with 75% of psychotropic medications^{98 Arehart-Treichel} and 25% of general medications^{99 Wang} metabolised by CYP450 2D6. CYP450 2C9 and 2C19 metabolise proton pump inhibitors, certain tricyclic antidepressants, barbiturates, beta-blockers, nonsteroidal anti-inflammatory drugs and warfarin.^{100 Borlak} One single antipsychotic, such as clozapine requires a combination of CYP450 1A2, 3A4, 2C9, 2C19, 2D6 enzymes for metabolism.^{101 Linnet}

Each CYP450 gene consists of two strands of DNA from each parent, with a variety of polymorphisms ranging from null/non-functional, partially active/diminished function, normal fully functioning, through to alleles which have multiple copies and therefore increased function. The phenotype i.e. metaboliser status of the individual, for the CYP450 system is determined by many factors including the co-prescription of cytochrome inhibiting drugs, iron status, general and liver health.

Extensive metabolisers (EMs) are “normal” efficient metabolisers, and are expected (unless under age 23) to be able to metabolise a “standard” medication dose which is determined but not defined by pharmaceutical companies based upon EMs. Poor metabolisers (PMs) are inefficient metabolisers with no metabolising activity, therefore the resulting medication toxicities rapidly cause iatrogenic side effects or adverse drug reactions (ADRs). Intermediate metabolisers (IMs) have diminished activity and are at greater risk as ADRs build up slowly and will appear later. Ultra rapid metabolisers (UMs) have higher than normal rates of metabolism which can either result in treatment being inefficient or with prodrugs result in high levels of prodrug toxic metabolites. The window of opportunity for a therapeutic level is determined by EMs. Toxicity and ineffective outcomes are determined by PMs, IMs and UMs. Persons who are PMs and/or IMs of psychiatric or general medications, and UMs of prodrugs are at risk of experiencing neurotoxic behavioural reactions due to the body’s inability to metabolise medications optimally.

Population frequency of genetic variations

CYP450 2D6 is a highly variable enzyme in different populations.

CYP450 2D6 PMs prevalence: Caucasians (5-10%)^{102 J de Leon, 103 Bradford}, Asian (0-2%)^{103 Bradford} African (6.3%)^{104 Bradford}, African American (14.5%)^{104 Bradford} and Black populations up to 19%.^{103 Bradford} East Asians (50%)^{104 Bradford} and Pacific Islanders (41%)^{104 Bradford} have the diminished CYP2D6*10.^{103 Bradford, 104 Bradford} Up to 29% in North Africa and the Middle East, are CYP2D6 UMs.^{102 J de Leon}

CYP2C19 PM prevalence: Europeans (3-6%),^{105 Kaneko} Asians (41%),^{106 Sistonen} and East Asians (up to 25%).^{102 J de Leon} Melanesian populations (up to 90%) PMs^{106 Sistonen} and persons from Vanuatu have a 79% rate of the diminished 2C19*2.^{105 Kaneko}

ADRs can occur with just one non-functional or one diminished function allele. For example, CYP1A2*1C, diminished function and CYP1A2*1D are associated with increased clozapine exposure and adverse reactions.^{107 Flockhart} It is important to note that ADRs are substrate specific in that an IM genotype enzyme at CYP2D6 will become a PM phenotype in the presence of an inhibitor of CYP2D6.^{108 Zourkova}

The CYP1A2*1K allele has diminished induction^{109 Aklillu} In 3 case studies, Asian patients prescribed clozapine experienced aggression and disruptive behaviour which improved when clozapine was discontinued.^{21 Mansour} Although the genotype of the Asian patients in the study is unknown, 25% of Asians^{110 Todesco} have CYP1A2*1C diminished induction and 41% are non functional at 2C19*2 or 2C19*3.^{106 Sistonen} 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.

Table 6: The Link between Genotype Status and Neurotoxic ADRs for CYP450, 5HTT-LPR and 5-HT Allele Variants when treated with antidepressant medications

NEUROTOXIC BEHAVIOURAL ADRs	CYP450 AND SEROTONERGIC GENETIC VARIANTS
Akathisia/agitation/ Restlessness	CYP450 2D6 and 2C19 non-functional alleles ^{44 Lucire} CYP450 2D6 and 2C9 diminished function alleles ^{44 Lucire} CYP450 2C19 ultra rapid multiple allele duplications ^{44 Lucire} CYP2C9 non-functional alleles ^{114 Piatkov et al 2012} 5-HTTLPR short allele ^{111 Perlis, 112 Spinelli} 5-HTR2A receptor variant ^{113 Murphy 2003}
Suicide/suicide risk	CYP450 2D6, 2C19 and 2C9 non-functional and diminished function alleles. ^{44 Lucire, 114 Piatkov et al 2012} CYP450 2D6 ultra rapid multiple allele duplications ^{44 Lucire} 5-HT1AC receptor variant ^{115 Sawiniec}
Homicide/attempted homicide	CYP450 2D6 and 2C19 non-functional ^{44 Lucire} CYP450 2D6 and 2C9 diminished function alleles ^{44 Lucire} CYP450 2C19 ultra rapid multiple allele duplications ^{44 Lucire}
Insomnia	5-HTTLPR short allele ^{111 Perlis}

NEUROTOXIC BEHAVIOURAL ADRs	CYP450 AND SEROTONERGIC GENETIC VARIANTS
Mania /delirium	CYP450 2D6 and 2C19 non-functional alleles ^{44 Lucire} CYP450 2D6 and 2C9 diminished function alleles ^{44 Lucire} CYP450 2C19 ultra rapid multiple allele duplications ^{44 Lucire} 5-HTTLPR short allele ^{111 Perlis, 116 Mundo}
Serotonin Syndrome	CYP450 2D6 IM ^{117 Sato}
Psychosis	CYP2D6 non- functional and diminished allele ^{114 Piatkov 2012}
Delusions	CYP2D6 diminished allele ^{114 Piatkov 2012}
Dysphoria	CYP2D6 non-functional allele and diminished function allele ^{114 Piatkov 2012}
Hallucinations	CYP2D6 non-functional allele and diminished function allele ^{114 Piatkov 2012}

“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”^{44 Lucire} 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 Zackrisson} 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 Zackrisson} Moreover UMs at CYP2D6 were over represented in the morgues as suicides and intoxications deaths.^{118 Zackrisson, 119 Ingleman-Sundberg}

Risperidone and CYP2D6 diminished function allele is associated with NMS.^{120 Ochi} Behavioural symptoms associated with NMS, which can also occur with SSRIs and SNRIs,^{121 Mullet} include aggression, agitation and violence.^{122 Kasantikul}

Antipsychotics and modern general medications, which are serotonergic, could cause similar neuropsychiatric behavioral reactions due to inefficient CYP450 metabolism and 5-HTT polymorphism.

Cannabis is predominantly metabolised though CYP450 3A4, 2C9, 2C19 and 2D6^{123 Watanabe, 124 Jiang, 125 Sohayla} and 50% of cannabis smokers who have accessed drug clinics have the heterozygous genotype of cytochrome P450 2D6*4.^{125 Sohayla} Persons with pharmacogenetic variations in these enzymes may be susceptible to neurotoxic behavioural reactions such as hallucinations, psychosis, akathisia, violence, suicide and homicide.

Table 7: Metabolic pathways of recreational and psychiatric drugs show the same CYP450 pathways are used.

RECREATIONAL DRUG	CYP450 ENZYMES				
	1A2	2D6	2C9	2C19	3A4
Cocaine meth/amphetamine	Inducer Substrate inhibitor	Substrate Substrate	inhibitor		
MDMA cannabis		Substrate Substrate	Substrate	Substrate	inhibitor
“ATYPICALS”	1A2	2D6	2C9	2C19	3A4
Olanzapine	Substrate	Substrate inhibitor	inhibitor	inhibitor	inhibitor
Quetiapine	Substrate	Substrate inhibitor		Substrate	Substrate
Risperidone		Substrate inhibitor ^b			Substrate inhibitor
Clozapine	Substrate inhibitor	Substrate inhibitor ^c	Substrate inhibitor	Substrate inhibitor	Substrate inhibitor inducer
NEW ANTIDEPRESSANTS	1A2	2D6	2C9	2C19	3A4
Fluoxetine		Substrate inhibitor ^a	Substrate inhibitor ^b	Substrate	Substrate inhibitor ^b
Paroxetine		Substrate inhibitor ^a	inhibitor ^c	inhibitor ^c	Substrate inhibitor ^b
Sertraline	Inhibitor ^c	Substrate inhibitor ^a	Substrate inhibitor ^b	Substrate	Substrate inhibitor ^c
“TYPICAL” ANTIPSYCHOTIC	1A2	2D6	2C9	2C19	3A4
Chlorpromazine	Substrate	Substrate inhibitor ^a			Substrate inducer

a weak, b intermediate and c strong inhibition. Weak inhibitors are strong in high doses
[126 Wynn, 127 Preissner](#)

An epidemiological survey found cannabis use was associated with a higher ratio of violence in the general population, compared with those with an SMI diagnosis.^{128 Johns} Users who have an inability to metabolise recreational drugs, will not be able to metabolise psychiatric drugs if prescribed in an attempt to ameliorate toxic induced reactions. 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 medications either inhibiting or inducing metabolism^{129 Armstrong} and prescribers need to be aware of interactions that can worsen behavioural reactions.^{130 Tredger} For example a variant of NMS secondary to drug interaction was incurred when donepezil was added to olanzapine with a patient already experiencing EPSE.^{131 Warwick} Omeprazole, proton pump inhibitor prescribed for gastric reflux, a common side effect of antipsychotics, is a CYP1A2 inducer.^{130 Tredger} When omeprazole was concurrently prescribed with clozapine the interaction caused a significant reduction of plasma clozapine levels,^{132 Spina} 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.^{44 Lucire} SSRIs and other antidepressants that are serotonergic agents have effects upon serotonin receptors or serotonin uptake.^{11 Jackson}

p.⁷² Deletion of long alleles in 5-HTT is associated with a ‘powerfully predicted non response’,^{133 Kim} and more adverse events.^{134 Murphy} The 5-HTTLPR short allele is associated with akathisia, insomnia, mania and delirium^{134 Murphy} and agitation^{111 Perlis, 112 Spinelli} and anxiety.^{112 Spinelli}

Allelic variation in the HTR2A gene has been reported to affect response to SSRIs and risk for adverse drug reactions, with paroxetine inducing agitation.^{113 Murphy} 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 Sawiniek}

Genotyping

Pharmaceutical companies use pharmacogenetics in drug clinical trials which are designed to exclude PMs from phase II onwards.^{135 Witte} This is achieved by using the genotyping test to screen for individual genetic polymorphisms.

As medication dose is determined from results based on EMs, when medications are marketed they show efficacy with minimal side effects. Although pharmaceutical companies do mention enzyme pathways in relation with a handful of drug-drug interactions, (pharmacokinetics), prescribers and health and social care practitioners may be misled into thinking that this is all there is and are unaware some persons do not have fully functioning metabolising pathways for every medication.

In the UK pharmacogenetics and the relationship between different rates of drug metabolism and the occurrence of side effects in patients is largely unknown. One implicit factor relates to pharmaceutical companies excluding facts pertaining to PMs/IMs in their mandatory Summary of Product Characteristics (SmPC) for each medication. The SmPC informs the British Medical Association who in turn compile the British National Formulary. Another factor is British Medical Schools, as “inadequate education both at undergraduate and postgraduate levels is a potential barrier to the widespread uptake of pharmacogenetic tests.”^{136 Baars, 137 Newman} Although the International Society of Pharmacogenomics (ISP) recommended four or more hours of pharmacogenetic teaching for undergraduate medical students, only 21% of medical schools met that quota.^{138 Higgs} Both the UK General Medical Council and NICE state pharmacogenetics is not in their remit (personal communication), which is in conflict with the safety of patients they have chosen to serve.

The European Medicines Agency (EMA), responsible for authorising medications in Europe, have recently issued guidelines to pharmaceutical companies with the aim of making medications safer in relation with drug development, pharmacogenetic testing and dosage for specific genetic populations.^{139 EMA} How the EMA will ensure their guidelines will be adhered to remains unknown.

Pharmacogenetic knowledge can be utilised in tailoring medication to the individual for antidepressant therapeutic efficacy^{140 Kirchheiner} and as a safeguard in preventing side effects.^{141 Schillevoort} Countries such as Sweden and America have facilities where psychiatrists are able to have their patients screened for genetic polymorphism in CYP2D6 and 2C19 prior to prescribing antidepressants and antipsychotics^{98 Arehart-Treichel, 142 Mrazek}

Genotype testing for 5-HTT can be used to determine patients’ response to SSRIs,^{143 Smeraldi, 144 Eichhammer} so preventing a non therapeutic response and neuropsychiatric reactions. Since many antipsychotic drugs have serotonergic activity, 5-HTT testing could benefit patients prescribed antipsychotics. The identification of patients who are likely to develop neurotoxic akathisia, violence, suicide, homicide or psychosis though genotyping is essential for safe practice in prescribing. Retrospective genotyping for psychiatric drugs is known to reduce the

financial outlay/cost for inappropriate medication and subsequent healthcare costs, ¹⁴⁵ Winner as although the genotyping test incurs a one off initial cost, it reduces treatment failure, subsequent toxic episodes and treatment expenses. ¹⁴⁶ van der Wiede

Apart from expensive hospital care, other costs in association with extended treatment, are likely to include UK’s Severe Disability Allowance, Employment and Support Allowance and Self Directed Support; lifelong costs which are likely to follow on from protracted treatment costs.

Ethnic Black Populations

Statistically, Black Minority and Ethnic (BME) populations have greater difficulty metabolising general and psychotropic medications compared with White and Asian populations. There is a higher frequency of lower metabolism at CYP450 2D6 in Black populations compared to Caucasians, particularly when they show 2D6*2 and 2D6*29, which is also more frequent in IMs. ¹⁴⁷ Gaedigk

Table 8: Variation of CYP450 2D6 metabolising ability in BME populations.

BME	POOR METABOLISERS	ULTRA RAPID METABOLISERS*
South Africans	18.8%	
Nigerians	8.6-8.3%	
Ghanaians	6%	
African – American	3.9%	2.4%
Zimbabwean	2%	
Tanzanian	2%	
American Black	1.9%	
Ethiopians	1.8%	29%

*UMs are at risk if the first metabolite is psychoactive. ¹⁴⁸ Abraham

BME groups are four times more likely to experience psychosis than Caucasians, ¹⁴⁹ NMH DU with African Caribbean people three to five times more likely than any other group being diagnosed with schizophrenia and admitted to hospital. ¹⁵⁰ MH Foundation BME patients are over represented in the UK’s Psychiatric Intensive Care Units (PICUs) and Low Secure Units. ¹⁵¹ Pereira 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. ¹⁵² Feinstein “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.” ⁹³ Bowers

Under the UK Mental Health Act, there is a disproportionately large representation of BME patients detained. 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. ¹⁵³ Samuel BME groups have more UK Community Treatment Orders (CTOs), enforced when patients have a history of violence than white populations. ¹⁴⁹ NMH DU and since their introduction in 2007, CTOs have increased from 2,134 to 4,220 in 2011-12, an increase of 98%. Although CTOs

were introduced in 2007 to save on the expense of formal detentions in hospital, between 2006-07 and 2011-12 detentions increased from 46.5 thousand to 51.5 thousand,^{154 hscic} a rise of 11%.

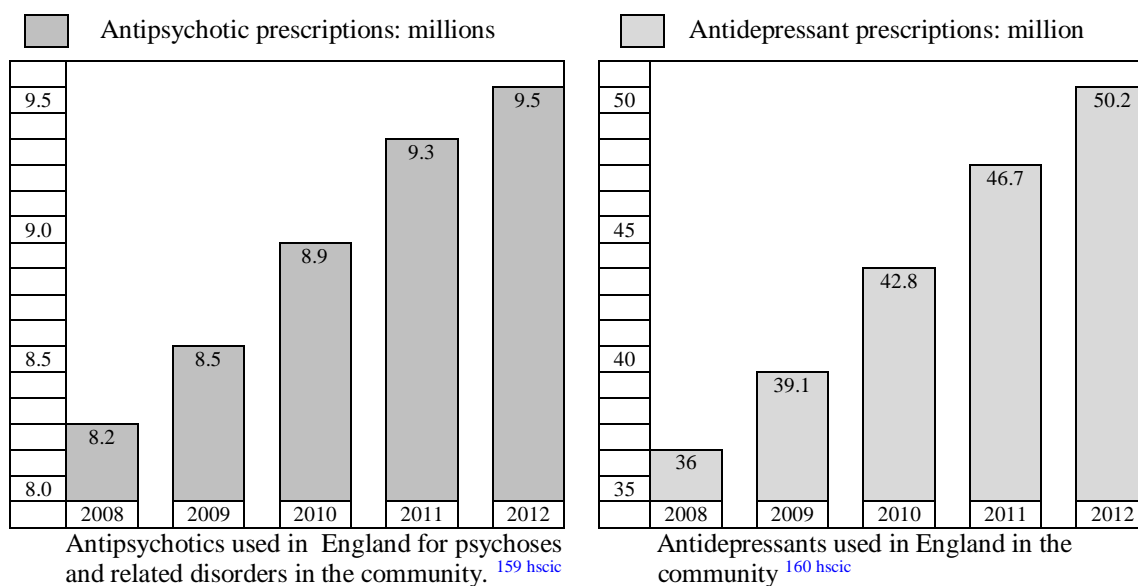
Kevin Gournay, Professor of Psychiatric Nursing, Health Services Research Department, Institute of Psychiatry, speculates on the unsatisfactory explanation between the relationship between schizophrenia diagnosis in connection with psychiatric inpatients, CTO and being black.^{155 Gournay} A plausible and satisfactory explanation is the higher incidence of PMs, IMs and UMs for CYP450 2D6 and 2C19 enzymes in BME predisposing to antipsychotic medications causing neuropsychiatric behavioural reactions including akathisia, aggression and violence.

Increased prescribing of psychiatric drugs

Increased prescribing for all medications^{156 Nuffield} has been associated with visits from pharmaceutical sales representatives.^{157 Spurling} In England psychiatric prescription drugs for mental disorders increased by 6.8% per year on average from 1998. The total increase is unknown as data for hospital prescribing in inpatient settings is not made available due to confidentiality.

Between 1998 and 2010, UK prescriptions for antipsychotics increased by an average of 5.1% every year^{158 Ilyas} which over twelve years, is a total increase of 60%. On average 325,000 additional antipsychotic prescriptions were prescribed each year from 2008 to 2012.^{159 hscic} Between 2008 and 2012, antidepressant prescriptions increased from 36 million to 50.2 million in the community, which is a total increase of 39.4% and an average of 3.5million additional prescriptions each year.^{160 hscic}

Figure 1: The rise in antipsychotic and antidepressant prescriptions.



The number of people accessing NHS mental health care has increased since data was collected and continues to rise^{161 hscic} with one explanation being the UK economic downturn.^{162 RCP} Other contributing factors will be the rise of all prescriptions^{156 Nuffield} including medications with serotonergic activity and increased cannabis use^{163 hscic} which for populations with CYP450 and 5-HTT polymorphisms, may induce neuropsychiatric reactions, incurring a mental health diagnosis.

Even though the UK's overarching treatment for mental illness is psychiatric prescribing, the DSM-IV-TR advocates with holding a diagnosis of mania or bipolar if a person has been taking medications, which induced iatrogenic neuropsychiatric

symptoms. This situation needs to apply to all medications before a mental illness is diagnosed. The DSM-IV-TR states “resolution of symptoms can take weeks or months and may require treatment (p. 191).”^{10 Breggin} For susceptible populations who have certain 5-HTT polymorphisms and are PMs, IMs, or UMs for prodrugs, subsequent treatment requiring the same metabolism, 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. When a person ingests a substance, medicinal, recreational or accidental that crosses the blood brain barrier, an unknown number up to a thousand neurotransmitters respond. If a few days later, the dose is changed up or down, or another drug is added, neurotransmitters respond to the challenge and after about 36 hours or however long the substance takes to cross the blood brain barrier, neurotransmitters respond again. During this period the patient has involuntary, unpredictable changes in thinking and behaviour, both of which are understandably abnormal. With UMs these changes at brain levels can happen during the course of a single day: with slower metabolisers the concentration of toxins increases over time. Eventually some sort of balance, or homeostasis, is reached with abnormal brain chemistry and this results in long term emotional and cognitive dysfunction. 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 continues in the absence of medicines that caused the initial neurotoxic reaction. 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. Normal thinking is unlikely, even impossible. In seriously depressed persons, treatment is with antidepressants in an attempt to induce a controlled manic shift, but if it goes too far, medication induced mania may supervene with violence induced due to chemical dysfunctioning.

Out of the innumerate neurotransmitters identified, the functions of which are still being researched, it is known the reciprocal interaction between the dopaminergic and serotonergic systems disturbed by dopamine inhibitors or serotonin enhancers leads to the disruption of homeostasis.^{164 Odagaki}

Serotonin and dopamine neurotransmitter functioning is connected with aggressive behaviour^{165 Berman} and dopaminergic and serotonergic medications are strongly associated with acts of violence.^{37 Moore} There are 14 different types of serotonin receptors^{11 Jackson p.220} that may be targeted by antidepressants and antipsychotics. Antipsychotics, clozapine, olanzapine, risperidone, quetiapine, amisulpride and clopixol have strong affinity for the serotonin 5-HT₂ receptor.^{11 Jackson, p.173}

Table 9: Adverse mental state changes associated with serotonin disruption.

Akathisia	hypomania
Suicidality	anxiety
agitation	confusion
Restlessness	hallucinations
Hyperactivity	aggression
delirium	irritability

^{10 Breggin, 166 Iqbal, 167 Boyer, 168 NZ Medsafe}

Serotonin Syndrome (SS), previously called serotonin toxicity, due to excessive serotonergic activity^{169 Robinson, 170 Sternbach} is associated with MAOI, TCA, SSRI and SNRI antidepressants. The following general medication groups, opiate analgesics, cough medications, muscle relaxants, antimigraine medications, weight-reducing drugs, antiemetics, mood-stabilizing drugs, antiviral drugs, antibiotics, anti-hypertensives, olanzapine, reserpine and recreational drugs are also associated with SS.^{166 Iqbal} This indicates many general medications are serotonergic agents. ‘Alteration in mental status, - ranging from agitation, excitement, irritability, hyperactivity, restlessness, anxiety, hypomania, confusion, lethargy, disorientation, delirium, hallucinations, and drowsiness to coma - is present in about 40% of patients with SS.’^{166 Iqbal}

All antipsychotic drugs have anticholinergic properties which disrupt the dopamine-acetylcholine equilibrium.^{171 Imperato, 172 Black} In response the body compensates, creating a rebound effect by producing and releasing more acetylcholine, which causes autonomic instability.^{173 Jackson} “This adaptation [to psychiatric drugs] replicates the effect of organophosphate poisoning [or indeed any chemical toxicity] whether by nerve gas, by insecticide, or by anti-Alzheimer’s pharmaceuticals, by over stimulating acetylcholine circuits of the brain.”^{173 Jackson}

Table 10: The symptom similarities of NMS and OP poisoning.

NEUROLEPTIC MALIGNANT SYNDROME	ORGANOPHOSPHATE POISONING
autonomic nervous system disturbance	autonomic instability
<i>aggression, agitation and violence</i>	<i>aggression</i>
<i>confusion</i>	<i>dementia, psychosis, anxiety, depression, tremors</i>
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

^{122 Kasantikul, 173 Jackson}

The overlapping features of autonomic instability of NMS and organophosphate poisoning 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 typical antipsychotics such as chlorpromazine, trifluoperazine and fluphenazine, was used initially as an insecticide in 1934.^{174 Whitaker}

Discussion

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.’^{175 Preda}

Persons treated for common mental health conditions that develop treatment emergent violence, aggression, homicide, suicidality, or mania and psychosis are diagnosed as SMI. Little consideration is given to the potential of these reactions being iatrogenic neuropsychiatric behavioural reactions from psychiatric/general medications or recreational drugs. In this situation the reaction is an organic, chemical toxic psychosis as opposed to a functional psychosis. Although the diagnosis is

associated with drug toxicity, which may be dose related or idiosyncratic to the person, the assumed diagnosis of SMI merely results in a social construct entailing traditional treatment being used as opposed to addressing the root problem of iatrogenic drug toxicity.

Drug toxicity occurs from CYP450 enzymes, 5-HTTLPR, 5-HTT polymorphisms and/or from disruption of homeostasis. Newer generations of antidepressants and the majority of all antipsychotics have strong serotonergic properties causing serotonin disruption, which is linked with akathisia and suicidal ideation. The fact that many general medications can incur SS suggests these medications also have serotonergic properties that cause neuropsychiatric behavioural reactions potentially leading to a mental health diagnosis. Whether the psychosis is toxic or functional, for people with CYP450, 5-HTTLPR and 5-HTT polymorphisms, subsequent treatment that involves the same metabolism, will not be therapeutic.

Ongoing toxic neuropsychiatric reactions and the use of polypharmacy in a vain attempt to stem toxic behavioural symptomatology, are likely to incur additional SMI diagnoses. Statistically, the numbers of patients who have been disabled by a drug that was supposed to have helped them remains unknown.

Drug companies have persuaded the public and clinicians more medication is needed and that a person should stay on medications indefinitely, which is reflected in psychiatric guidelines. It is difficult to stop taking antidepressants and antipsychotic medication because of potential treatment emergent withdrawal akathisia. When a person has been prescribed antipsychotic medications for a long time, supersensitivity psychosis supervenes^{176 Chouinard} confounding the diagnostic skills of all but the best read psychiatrists.

Conclusion

Antidepressants, antipsychotics and some modern general medications can cause toxic akathisia, which may predispose to violence whether directed towards self (suicide) or others (homicide). Persons, who are treated with antidepressants for common mental health disorders, may be subjected unwittingly to toxic suicidal and homicidal ideation. Likewise, persons who have no history of a mental health condition who are prescribed modern general medications may experience akathisia, EPSE, aggression, depression, suicidal ideation, psychosis and mania, all of which may contribute to violence.

Neurotoxicity is not understood for the iatrogenic condition that it is in psychiatry, and a diagnosis of mental illness made by the unwary who do not recognise the symptoms of iatrogenic neurotoxicity, can easily be mistakenly applied.

With the increasing use of antipsychotic, antidepressant and general modern medications, it is reasonable to expect an increased amount of violent behaviour amongst those with a mental health condition as well as those who have no history of a mental health condition. It is hypothesized the rise in violence for mental health conditions treated with antidepressants and antipsychotic medications will escalate, whether in the community, in acute wards, secure units, prisons or outpatient units. Increased admissions to the UKs PICUs and increased use of Mental Health Act detentions and Community Treatment Orders are envisaged.

Antipsychotics can cause violence, which needs to be considered not as an indication of how the SMI condition can worsen, but be recognised as iatrogenic akathisia. This can also relate to antipsychotic withdrawal. The common factor of aggression in OP poisoning and NMS is striking, and although aggression is a known symptom of OP poisoning, acetylcholine disruption stemming from antipsychotic

medications is not acknowledged as a cause of violence in SMI. Enforced legal treatment for SMI is unjust and promotes induced, although unwitting, psychological abuse towards psychiatric patients when persons are not able to metabolise medication treatments efficiently. This situation applies to all persons whatever their ethnicity.

The prevention of violence amongst susceptible persons with genetic variations is paramount and achieved by adopting the practice of genotype testing prior to treatment with antidepressant and antipsychotic medications as well as serotonergic and dopaminergic general medications. Increased pharmacological awareness of medication/drug toxicities within general and psychiatric training and practice by all health and social care practitioners would play a big part in reducing violence and dependence upon the mental health and welfare benefits system. Meanwhile, all prescribers, health and social care practitioners need to be educated about the different rates of metabolism in relation with how ADRs arise, the presentations of akathisia and the associated symptoms in the role of violence. Follow-up consultations and fully informing patients about akathisia, can prevent avoidable disastrous consequences whilst ensuring patient, professional and public safety.

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