

Neuroleptic Awareness

Part 8

Neuroleptic Drugs and Violence

Introduction

The treatment for Severe Mental Illness (SMI) is neuroleptic medication and violence has been established in people with a mental health diagnosis.

In patients with schizophrenia, 13.2 % experienced at least one violent offence compared with 5.3% of the general population. A greater risk of violence, 27.6% has been attributed to patients with substance abuse compared to 8.5% without substance use.

Source: Fazel S, et al, (2009) <http://www.ncbi.nlm.nih.gov/pubmed/19454640>

Violence is also reported with command hallucinations: 48% experienced harmful or dangerous actions, this increased to 63% in medium secure units and was significantly higher, 83%, in the forensic population.

Source: Birchwood et al. (2011) <http://www.biomedcentral.com/1471-244X/11/155/>

People who are classified as SMI i.e. with schizophrenia or bipolar often experience violent incidents *following* a diagnosis of SMI, even though they don't consume alcohol or use street drugs, nor having a past history of violence or command hallucinations to harm others.

The purpose of this document is to provide a referenced explanation of how neuroleptic medications are a potential cause of violence, from a physiological perspective due to the disruption of neurotransmitters and pharmacogenetic variants.

Part 1. Neuroleptic Disruption of Neurotransmitters

Part 2. Neuroleptics and Pharmacogenetic Variants

Part 1. Neuroleptic Disruption of Neurotransmitters

The first part of this document has the following structure:

- Violence
- Neuroleptic Adverse Effects on Behaviour
- Neuroleptic Withdrawal Adverse Effects on Behaviour
- Neurotransmitter Functioning and Behaviour
 - Serotonin disruption
 - Noradrenaline/Norepinephrine disruption
 - Acetylcholine disruption including Neuroleptic Malignant Syndrome and Organophosphate Poisoning
- Increased prescribing of neuroleptic as a risk for increased violence

Violence

Violence is an important issue.

In three acute psychiatric units in Australia, it was reported, **“58 % of the incidents were serious violent incidents.”**

Source: Owen C. et al, (1998) <http://ps.psychiatryonline.org/article.aspx?Volume=49&page=1452&journalID=18>

In an attempt to address psychiatric violence in the UK, NICE has a full **Clinical Guideline: “Violence. The short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments”** <http://www.nice.org.uk/nicemedia/live/10964/29715/29715.pdf>

Although NICE addresses many issues in it’s guidelines, it omits the following potential causes of violence:

- Neuroleptic medications - due to neuroleptic disruption of neurotransmitter circuits such as dopamine, serotonin and acetylcholine.
- Pharmacogenetics – the issue of inefficient neuroleptic metabolising.

Neuroleptic Adverse Effects on Behaviour

The next pages list those adverse affects of neuroleptics that are related to behavioural changes.

Toxic adverse reactions include **agitation, akathisia, restlessness, irritability and violence**. **Akathisia** is a predisposing factor to violence.

Source: Crowner ML, et al (1990) <http://www.ncbi.nlm.nih.gov/pubmed/1973544>

Restlessness, agitation and irritability are all symptoms of **akathisia** - an extreme, **involuntary** internal physical and emotional restlessness.

Any untoward disrespectful attitudes or verbal communications could trigger violence when there is an existing precondition such as akathisia, restlessness, agitation and irritability. When people are agitated or irritable, they are less able to cope with disrespectful mannerisms and are more prone to flare up with a violent response.

Neuroleptic Adverse Effects on Behaviour

A marked increase of violence occurred with patients prescribed moderately high-doses of haloperidol. *Source: John N. Herrera et al (1998)*
<http://psychrights.org/research/Digest/NLPs/RWhitakerAffidavit/HerreraNeurolepticsandViolence.PDF>

Clozapine has played a role in causing aggression and disruptive behaviour in Asian patients. *Source: Mansour, Willan and Follansbee (2003)*
http://bapauk.com/doc/Deteriorationofpsychosisinducedbyclozapine_41.doc

Both the older “typical” and the newer “atypical” neuroleptics are associated with behavioural adverse reactions.

“Newer antipsychotics did not reduce violence more than perphenazine.”
Source: Jeffrey W. Swanson et al, (2008) <http://bjp.rcpsych.org/content/193/1/37.full>

Neuroleptic Adverse Effects on Behaviour

For Typical Neuroleptics:

| Typical Neuroleptics | Adverse Reactions Related to Violence |
|-----------------------------|--|
| Clopixol | Agitation & akathisia |
| Haloperidol | Restlessness, agitation and violence |
| Stelazine | Restlessness |
| Sulpiride | Restlessness & akathisia |

Information sourced from Drug Monographs, Prescribing information and NICE 2007 – 2012.

John N. Herrera et al (1998) <http://psychrights.org/research/Digest/NLPs/RWhitakerAffidavit/HerreraNeurolepticsandViolence.PDF>

Jerome L. Schulte, (1985) <http://psychrights.org/research/Digest/NLPs/RWhitakerAffidavit/Schulte.PDF>

Neuroleptic Adverse Effects on Behaviour

For Atypical neuroleptics:

| Atypical Neuroleptics | Adverse Reactions Related to Violence |
|------------------------------|--|
| Abilify | Restlessness, agitation and akathisia |
| Amisulpride | Agitation |
| Clozaril | Akathisia and agitation |
| Olanzapine | Restlessness and agitation |
| Paliperidone/Invega | Akathisia and aggression |
| Quetiapine | Akathisia and irritability |
| Risperidone | Agitation |
| Sertindole | Akathisia |
| Zotepine | Akathisia |

Information sourced from Drug Monographs, Prescribing information and NICE 2007 – 2012.

Neuroleptic Adverse Effects on Behaviour

Observations in prisons have also associated neuroleptic treatment with increased aggressive behaviour:

Inmates were better able to control their aggression until they received neuroleptics and then the aggression rate almost tripled.

Source: Workman and Cunningham (1975) page 65

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2274756/pdf/canfamphys00332-0065.pdf>

Neuroleptic Withdrawal Adverse Effects on Behaviour

Furthermore there is the issue of violence experienced on withdrawal of neuroleptics. Irritability and agitation has been reported in association with neuroleptic withdrawal. *Source: MIND*

http://www.mind.org.uk/help/medical_and_alternative_care/making_sense_of_coming_off_psychiatric_drugs

And a direct reference has linked akathisia following the withdrawal of a depot in an inpatient setting. *Source: Theodore Van Putten, (1975)*

<http://psychrights.org/research/Digest/NLPs/RWhitakerAffidavit/VanPuttenManyFacesofAkathisia.PDF>

In order to prevent violence in association with akathisia and withdrawal, in either inpatient, prison or community settings, this process needs to be undertaken by a professional or lay person who is able to have a humanistic relationship thereby avoiding any antagonising behaviour. Irritability, agitation and akathisia need to be recognised as reactions to neuroleptic withdrawal.

Neurotransmitter Functioning influences Violent Behaviour

Fundamentally, human aggressive behaviour is determined by neurotransmitter functioning.

“A rich literature exists to support the notion that monoamine (i.e. **serotonin, dopamine, and norepinephrine**) neurotransmitter functioning is related to human aggressive behaviour.”

*Source: Berman ME, Coccaro EF. “Neurobiologic correlates of violence: relevance to criminal responsibility.” Behav Sci Law. 1998 Summer;16(3):303-18. Review.
<http://www.ncbi.nlm.nih.gov/pubmed/9768463>*

Neuroleptics Disrupt Neurotransmitter Functioning

Chronic neuroleptic treatment causes unpredictable reactions due to dysregulation and disruptions between dopamine, serotonin and acetylcholine neurotransmitters.

Jackson's *First* Law of Biopsychiatry states:

“For every action, there is an unequal and frequently unpredictable reaction.”

*Source: Jackson, Grace E. MD, Appendix D, Transcript of
“What Doctors May Not Tell You About Psychiatric Drugs”
Public Lecture, Centre for Community Mental Health - UCE Birmingham June 2004*

Neuroleptics Disruptive Influence on Serotonin

Some neuroleptics are known as serotomimetic drugs, affecting serotonin receptors – some block the receptors and some make them more active.

Dopamine, serotonin and all other neurotransmitter circuits are interdependent and any disturbance in one will result in an imbalance in them all, disrupting normal functioning.

"There are 14 different types of serotonin receptors that may be targeted by neuroleptics, with risperidone, clozapine, olanzapine, quetiapine and clopixon especially affecting the serotonin 5-HT₂ receptor."

*Source: Jackson Grace E.(2005) [Rethinking Psychiatric Drugs: A Guide for Informed Consent](#).
Bloomington, IN: Author House.*

Neuroleptics Disruptive Influence on Serotonin

Neuroleptic drugs may cause serotonin toxicities such as Serotonin Syndrome causing changes in mental status.

The reciprocal interaction between the dopaminergic and serotonergic systems disturbed by either dopaminergic blockers or serotonergic enhancers leads to the disruption of homeostasis.

Source: Odagaki (2009) <http://www.benthamscience.com/cds/samples/cds4-1/0013CDS.pdf>

Serotonin Disruption and Increased Violence

Research indicates that serotonin disruption is associated with increased violence in animals.

Reduced levels of a specific serotonin metabolite (5-HIAA) in cerebrospinal fluid has been linked with increased aggression in both dogs and male rhesus macaques.

Sources: Reisner I, et al, (1996) <http://www.ncbi.nlm.nih.gov/pubmed/8861609>

Mehlman P, et al (1990) <http://www.ncbi.nlm.nih.gov/pubmed/7522411>

Low concentrations of 5-HIAA have been consistently reported to be associated with impulsive destructive behaviours, aggression and violence in different cultures.

Source: Brown & Linnoila (1990) <http://www.ncbi.nlm.nih.gov/pubmed/1691169>

Serotonin Disruption and Increased Violence

“Impulsive violence is closely linked to serotonergic function and to several brain regions”

Source: Muller JL et al (2004) <http://www.ncbi.nlm.nih.gov/pubmed/15570500>

“Given the fact that low and high serotonin levels have been linked to impulsivity.... it is difficult to know which of these changes play the most important role in treatment emergent violence.”

*Source: Jackson Grace E.(2005) [Rethinking Psychiatric Drugs: A Guide for Informed Consent](#).
Bloomington, IN: Author House.*

The serotonin system and its interactions with other neurotransmitters are complex. And full information is difficult to find, however there are clear research papers, which show that serotonin and aggression are related.

Serotonin Disruption and Behavioural Changes

Low and high serotonin levels have been linked to impulsivity and treatment emergent violence.

Serotonin disruption is associated with the following adverse toxic effects:

| | |
|-------------------|----------------------|
| Akathisia | Irritability |
| Suicidality | Violence |
| Arson | Aggression |
| Violent Crime | Self Destructiveness |
| Impulsive Acts | Agitation |
| Hostility | Violent Suicide |
| Argumentativeness | |

Sources: Breggin(2003/4) <http://www.breggin.com/31-49.pdf>,

Pert CB. Ph.D., (2001) <http://ecommerce.drugawareness.org/Ribbon/SSRIMeds.html>

Neuroleptics and Noradrenaline Disruption

Neuroleptics additionally affect the norepinephrine neurotransmitter which is linked with akathisia.

Source: Naveed Iqbal, MD, et al, (2007)

<http://www.cnsspectrums.com/aspx/articledetail.aspx?articleid=1262>

“The increased noradrenaline turnover seen after haloperidol may have important implications regarding...the mechanism of akathisia induction.”

Source: Hall LM et al (1995) <http://www.ncbi.nlm.nih.gov/pubmed/7543647>

The link between akathisia and violent behaviour was formally recognised in the late 1970s.

Source: GB. Leong, M.D. and JA Silva, M.D.(2003)

http://library-resources.cqu.edu.au/JFS/PDF/vol_48/iss_1/JFS2002173_481.pdf

Neuroleptics Disruptive Influence on Acetylcholine

An important function of the acetylcholine neurotransmitter is the control of psychological defence mechanisms including fight or flight responses. Such responses are impulsive and naturally include aggression and violence.

Certain antipsychotic drugs have strong anticholinergic properties, which means they block and disrupt the acetylcholine neurotransmitters. The body compensates and responds by making and releasing **more acetylcholine**.

Source: Grace Jackson MD (2009) [Drug Induced Dementia. A Perfect Crime](#) Bloomington, IN: Author House.

Acetylcholine Disruption and Increased Violence

Scientific research in animals depicts **excessive acetylcholine** is responsible for aggressive responses such as defensive rage and violence:

Siegel A, Bhatt S. (2007) <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2435345/>

Stefan M. Brudzynski, et al (1990) <http://www.ncbi.nlm.nih.gov/pubmed/2293258>

Graeff FG. (1994) <http://www.ncbi.nlm.nih.gov/pubmed/7916235>

Neuroleptics block dopamine receptors resulting in an absolute decrease of dopamine and a relative abundance of acetylcholine.

Sources: Donald W. Black, Nancy C. Andreasen - *Introductory Textbook of Psychiatry* - (2011)
5th Edition p.544 American Psychiatric Publishing Inc.

Imperato (1993) <http://jpet.aspetjournals.org/content/266/2/557.abstract>

Excessive acetylcholine is known to trigger aggression and violence.

**Neuroleptic → Disrupted dopamine-acetylcholine equilibrium →
Relative increase acetylcholine → Aggression/Violence.**

Acetylcholine in Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS) is an adverse effect of neuroleptics, a potentially fatal condition with up to 76% mortality rate.

The symptoms of **NMS** include **aggression, agitation and violence.**

Sources: Grace Jackson MD (2009) *Drug Induced Dementia. A Perfect Crime*
Bloomington,IN: Author House.

Kasantikul D, Kanchanatawan B, (2006)<http://www.ncbi.nlm.nih.gov/pubmed/17214072>

Relatively new research associates **NMS** with **elevated acetylcholine.**

Source: Tanya C Warwick, et al, (2008)

<http://www.nature.com/nrneurol/journal/v4/n3/full/ncpneuro0728.html>

Acetylcholine in Organophosphate Exposure

Organophosphates are chemicals that form the basis of many insecticides, herbicides and nerve gases. They block the action of the body's acetylcholin-esterase enzyme, which breaks down acetylcholine so it can be processed and recycled. If the action of this enzyme is blocked, **excessive acetylcholine** accumulates in the nervous system.

Acetylcholine in Organophosphate Exposure

Prolonged and repeated exposure to Organophosphates results in ***Chronic Organophosphate-Induced Neuropsychiatric Disorder (COPIND)*** e.g. in farmers who handle pesticides, due to chronic **Organophosphate Poisoning (OP) COPIND** behavioural symptom changes include: **Hostility, Anger, Aggression and Violence.**

Sources: Davies et al, (2000) <http://www.national-toxic-encephalopathy-foundation.org/oppest.pdf>
Singh S, Sharma N. (2000) <http://www.neurologyindia.com/text.asp?2000/48/4/308/1510>

Since **Organophosphate Poisoning (OP)** results in **excessive acetylcholine**, which is linked with aggression and violence in animals, the behavioural changes in **COPIND** are highly likely due to **excessive acetylcholine**.

Linking Neuroleptic Malignant Syndrome and Organophosphate Poisoning

The symptoms of **NMS** and **OP** are similar...(See following page)

In both **NMS** and **OP** the replication of symptoms is due to **autonomic instability** and stems from disruption of the acetylcholine circuits and transmitters of the **Autonomic Nervous System**, involved with vital involuntary functions.

Autonomic Instability - includes profuse sweating, high blood pressure, low blood pressure, respiratory distress, drooling, urinary or faecal incontinence, increased and decreased heart rate. *Source: Grace Jackson MD (2009) "Drug induced Dementia a perfect Crime." Bloomington, IN: Author House.*

Linking Neuroleptic Malignant Syndrome and Organophosphate Poisoning

The symptoms of **NMS** and **OP** correspond - often with different words to describe a symptom; and are outlined below.

| Neuroleptic Malignant Syndrome | Organophosphate Poisoning |
|---|--|
| <i>Aggression, agitation and violence</i> | <i>Aggression</i> |
| Autonomic nervous system disturbance | Autonomic Instability |
| Muscle rigidity | Paralysis, Dystonia, Tremors, Cranial nerve palsy, polyneuropathy |
| Muscle breakdown | Weak respiratory and limb muscles |
| Coma, alterations of consciousness | Loss of consciousness |
| Confusion | Dementia, psychosis, anxiety, depression |
| Fever | Seizures |

Sources: G Jackson (2009) *“Drug induced Dementia a perfect Crime.”*
 Duangjai Kasantikul MD et al, (2006) <http://www.ncbi.nlm.nih.gov/pubmed/17214072>

Acetylcholine Conclusion - Organophosphates, Neuroleptics and Violence

Organophosphate Poisoning results in over stimulated acetylcholine neuro-circuits and systems. The action of neuroleptics is similar.

It is generally accepted that Organophosphate Poisoning results in behavioural changes including violence.

Despite research to show that neuroleptics are associated with disrupted acetylcholine, it is not yet generally accepted that neuroleptics are a potential cause of violence.

Acetylcholine Conclusion - Organophosphates, Neuroleptics and Violence

Antipsychotic/neuroleptic drugs have strong anti-cholinergic properties. Long term use causes behavioural changes, which replicate the same behavioural changes occurring in chronic Organophosphate Poisoning:

“This adaptation (to psychiatric drugs) replicates the effect of organophosphate poisoning (whether by nerve gas, by insecticide, or by anti-Alzheimers pharmaceuticals) by over stimulating acetylcholine (transmission and) circuits of the brain”.

Source: Grace Jackson MD (2009) “Drug induced Dementia a perfect Crime.” Authorhouse

Increased Prescribing of Neuroleptics

Over the last years there is a distinct increase in use of neuroleptic medications. More and more neuroleptics are being prescribed to people as part of treatment for mental health issues.

Antipsychotics increased by 5.1% (95% CI 4.3–5.9) per year 1998 – 2010.

That is a total increase of 60% over 12 years.

*Source: Trends in prescriptions and costs of drugs for mental disorders in England, 1998–2010
Stephen Ilyas and Joanna Moncrieff (2012)*

<http://bjp.rcpsych.org/content/early/2012/03/10/bjp.bp.111.104257.abstract>

Increased Prescribing of Neuroleptics

The approximate number of neuroleptic and depot (injection) prescriptions used in the community in England:

2008 – 7.0 million

2009 – 7.3 million

2010 – 7.6 million

2011 – 7.9 million

Source: NHS The Information Centre for Health and Social Care “Copyright © 2012, Re-used with the permission of the Health and Social Care Information Centre”. www.ic.nhs.uk

The data for the number of neuroleptic prescriptions in inpatient settings is not made available due to confidentiality issues. So the actual total increase of neuroleptic prescriptions in the UK is unknown.

Increased Prescribing: Increased Violence

As outlined in the first section of this document, neuroleptics are a possible cause of violence.

With increased prescribing of neuroleptic medications, it is reasonable to expect increased violence for those with a severe mental health diagnosis.

Since neuroleptic prescriptions are increasing by 300,000 per year in the UK, it is hypothesized the rise in violence for neuroleptic 'treated' patients will escalate: whether this is in the community, acute wards, secure units, outpatients or prisons.

Part 2. Neuroleptics and Pharmacogenetic Variants

The second part of this document has the following structure:

- Introduction to Pharmacogenetics regarding Neuroleptics
- Pharmacogenetics and Ethnic Black Populations
- Black populations and Psychiatric Intensive Care Units (PICUs)
- Black populations, detention under the UK Mental Health Act and UK Community Treatment Orders (CTOs)
- Pharmacogenetics as an explanation for Black Over-representation in Psychiatric Intensive Care Units, Mental Health Act detentions and for Community Treatment Orders.

Pharmacogenetics and Neuroleptics - Introduction

Pharmacogenetics is the science of how drugs are broken down and used – i.e. metabolised in the body, mainly in the liver, by the genetically diverse Cytochrome P450 (CYP450) enzyme system and other drug metabolising systems.

Extensive Metabolisers are efficient metabolisers and side effects do not build up.

Poor, Intermediate and Ultra Rapid Metabolisers are genetically inefficient at metabolising drugs.

Poor Metabolisers, have no metabolising activity whatsoever so drug toxicities causing side effects build up.

Intermediate Metabolisers have approximately 50% drug metabolising capacity and experience less side effects than Poor Metabolisers.

<http://www.healthanddna.com/healthcare-professional/dosing-recommendations.html>

Pharmacogenetics and Neuroleptics – Introduction

Ultra Rapid Metabolisers/ Hyperinducers have higher than normal rates of drug metabolism and “For prodrugs ultra metabolizers may also be at increased risk of drug-induced side effects due to increased exposure to active drug metabolites”

<http://www.healthanddna.com/healthcare-professional/p450-2d6-genotyping.html>

Prodrugs are inactive until they are broken down in the body and converted to their active drug form. <http://en.wikipedia.org/wiki/Prodrug>

Pharmacogenetics and Neuroleptics - Introduction

Neuroleptic drugs are metabolised through **CYP450** enzymes e.g. **CYP450 1A2, 2D6** and **2C19**. A single neuroleptic can necessitate a combination of **CYP450** enzymes for metabolisation.

All SMI patients who are **Poor** and/or **Intermediate Metabolisers** of neuroleptics and **Ultra Metabolisers** of neuroleptic prodrugs; e.g. paliperidone the active metabolite of risperidone; will inevitably suffer neurological and behavioural changes due to toxicities incurred from the inability to metabolise neuroleptics efficiently. Polypharmacy further compounds the toxicities.

CYP450 1A2 Metabolising Pathway

CYP450 1A2 enzyme pathway has many variants and metabolises olanzapine and haloperidol and is the major metabolising enzyme for clozapine.

CYP1A2*1C and *1D Poor Metaboliser genotypes have been associated with increased clozapine exposure and adverse reactions.

Sources: *Clinical and Translational Science: Principles of Human Research* by David Robertson and Gordon H. Williams Academic Press Inc; (16 Jan 2009) Chapter 21 page 303

CYP1A2*1K is also **Poor Metaboliser** genotype.

Source: <http://www.imm.ki.se/CYPalleles/cyp1a2.htm>

25% of Asians have **CYP1A2*1C Poor Metaboliser** genotype.

Source: Todesco (2003) et al <http://www.ncbi.nlm.nih.gov/pubmed/12851801>

CYP450 1A2 Metabolising Pathway

Clozapine played a role in causing aggression and disruptive behaviour in Asian patients whose behaviour had a marked improvement when clozapine was removed from their treatment regime. *Source: Mansour, Willan and Follansbee (2003) http://bapauk.com/doc/Deteriorationofpsychosisinducedbyclozapine_41.doc*

The genotype of the Asian patients in the study is unknown. Therefore it is possible these patients were **CYP1A2*1C** or ***1D** or ***1K** or a combination of these of these **Poor Metaboliser** genotypes.

Additionally **15-20%** Asians are **Poor Metabolisers** for **CYP2C19** and **2%** are **Poor Metabolisers** for **CYP2D6**. **CYP2C19** and **CYP2D6** metabolise clozapine as well as **CYP1A2**: any of these combinations are possible and could have predisposed to disruptive behaviour.

Source: Sandra A. Jacobson, Ronald W. Pies, Ira R. Katz [Clinical Manual of Geriatric Psychopharmacology](#) (2007) American Psychiatric Press Inc.; 1st edition p.44-45

CYP450 2D6 Metabolising Pathway and Neuroleptics

75% of all psychotropic drugs, including neuroleptics, are metabolised via CYP450 2D6. Source: Arehart-Treichel J.(2005) <http://pnhw.psychiatryonline.org/content/40/10/33.1.full>

CYP450 2D6 is a highly variable enzyme with a significant percentage of the population being **Poor, Intermediate** or **Ultra Metabolisers** i.e. inefficient metabolisers, of drugs broken down via this enzyme pathway.

CYP450 2D6 inherent genetic factor variability is linked to poor therapeutic response and adverse reactions.

Violence in relation with serotonin toxicity/akathisia has been linked with pharmacogenetic **CYP450 2D6** drug metabolising variants.

Source: Lucire & Crotty (2011) http://www.dovepress.com/articles.php?article_id=7993

Pharmacogenetics and Ethnic Black Populations

Due to genetic variations there is higher incidence of **Poor Metaboliser** and **Ultra Metaboliser** status in **Black** populations, compared with White and Asian populations for the **CYP 450 2D6** pathway.

“The prevalence of poor metabolizers in Black populations (*for CYP 2D6*) has been estimated from **0 to 19%**, compared with consistent reports of poor metabolizer status in Caucasians (5–10%) and Asians (0–2%)”

Source: L. DiAnne Bradford et al (1998) <http://www.ncbi.nlm.nih.gov/pubmed/11281961>

Pharmacogenetics and Ethnic Black Populations

Recalling that **75%** of neuroleptic medications are metabolised via **CYP450 2D6**, the following table shows the variation of metabolising ability in black ethnic populations for **CYP450 2D6**.

| | Poor Metabolisers | Ultra 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% |

Source: Abraham BK, Adithan C. (2001) <http://medind.nic.in/ibi/t01/i3/ibit01i3p147.pdf>

Pharmacogenetics and Ethnic Black Populations

29% of Ethiopians and **2.4%** of North African Americans are **Ultra Metabolisers** via **CYP450 2D6** pathway.

Source: Abraham BK, Adithan C.(2001) <http://medind.nic.in/ibi/t01/i3/ibit01i3p147.pdf>

Furthermore, **10-20%** of Africans are **Poor Metabolisers** and **5%** are **Ultra Metabolisers** via **CYP450 2C19**.

<http://www.healthanddna.com/healthcare-professional/p450-2c19-genotyping.html>

Statistically black populations have difficulty in metabolising medications via the CYP450 pathways.

People from BME groups living in the UK are more likely to be diagnosed with Mental Health problems and admitted to hospital.

Source: Mental Health Foundation - Black and Minority Ethnic Communities

<http://www.mentalhealth.org.uk/help-information/mental-health-a-z/B/BME-communities/>

Psychiatric Intensive Care Units

In Psychiatric Intensive Care Units (PICU), there is clear over-representation of black ethnic patients. *Source: Stephen Pereira et al, (2006)*
<http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=651260>

"Fifty-five percent of PICU admissions came from ethnic minorities (compared with 25.6% of total hospital admissions and 20.9% of the local catchment area population aged between 16 and 65 years)"

Source: Feinstein and Holloway (2002) <http://isp.sagepub.com/content/48/1/38.short>

“Typical PICU patients are male, younger, single, unemployed, suffering from schizophrenia or mania, from a **Black Caribbean** or **African** background, legally detained, with a forensic history. **The most common reason for admission is for aggression management**” *Source: Len Bower et al, (2008)*

<http://www.kcl.ac.uk/iop/depts/hspr/research/ciemh/mhn/projects/litreview/LitRevPICU.pdf>

UK Mental Health Act Detentions

There is also a disproportionately large representation of Black Minority and Ethnic (BME) origin when considering those who are legally detained under the UK Mental Health Act.

The proportion of black and black British people legally detained rose by 9.7%, with a 9% rise 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 from 2007/8 to 2008/9.

This disparity grew and 53.9% of black/black British inpatients spent time compulsorily detained, as did almost half of mixed-race inpatients and over 40% of Asian/Asian British inpatients, compared with 31.8% of all psychiatric inpatients who spent some time detained during the year.

Source: "Mental Health Act detentions rise sharply for BME groups" Community Care (2009)
<http://www.communitycare.co.uk/Articles/25/11/2009/113253/mental-health-act-detentions-rise-sharply-for-bme-groups.htm>

UK Community Treatment Orders

BME Groups have more Community Treatment Orders than white populations.

Source: BME Groups and Mental Health – Presentation and Evidence to the Centre for Social Justice Mental Health Review 18 October 2010. www.nmhdu.org.uk/silo/files/bme-groups-and-mental-health-.doc

A person having mental health treatment and history of violence is one of the legal conditions in which a CTO can be enforced. Mental health treatment most likely involves neuroleptic ‘treatment’.

Pharmacogenetics and BME Groups in Psychiatric Treatment

The last three slides show:-

- More BME on PICUs where aggression is a problem
- More BME in Mental Health Act detentions
- More BME in Community Treatment Orders

“There is a possible relationship for psychiatric in-patients between compulsory detention, disturbed behaviour, depot medication and being black, which is not satisfactorily explained by diagnosis alone.”

Source: Violence: The Short-Term Management of Disturbed/Violent Behaviour in Psychiatric In-patients and Emergency Departments Guideline, Appendix 1: Ethnicity review evidence tables. p.447 http://www.rcn.org.uk/_data/assets/pdf_file/0003/109812/003017_appendices.pdf

The higher incidence of mental health problems in black populations is most likely due to the higher incidence of Poor, Intermediate and Ultra Metabolisers and the associated problems with metabolising medications.

However, whatever the nationality, when individuals are Poor and Intermediate Metabolisers and Ultra Rapid metabolisers for prodrugs, the impact of neuroleptics in triggering akathisia, aggression or irritability is indiscriminate.

Synopsis

Neuroleptics can be a cause of violence due to neurotransmitter disruption.

Violence must be considered not simply as an indication of how deeply schizophrenia /bipolar illness can worsen, but as an adverse effect of neuroleptic treatment.

People who are inefficient metabolisers are likely to suffer more severe adverse effects and become violent or aggressive.

BME populations have a higher incidence of inefficient metabolisers and as such a higher incidence of violence leading to PICU admissions and Mental Health Act detentions.

Conclusion

There is a larger incidence of violence in people with a severe mental health diagnosis than in the general population. The severely mentally ill are invariably treated with neuroleptic medication which itself can be the cause of violence since neuroleptic medications disrupt neurotransmitter functions. This disruption of neurotransmitter functioning can precipitate violent behaviour. Withdrawal of neuroleptic medication - due again to the disruption of neurotransmitters - is also associated with violence.

Pharmacogenetics show that some people are unable to metabolise neuroleptic medication and this inability can result in further disruption of neurotransmitter functioning with a likelihood of increased violence.

The inability to metabolise neuroleptic medication is particularly prevalent in BME populations. As a consequence this population experience more violence which is confirmed in practice by an over representation of BME individuals, both on Psychiatric Intensive Care Units (PICUs) where a common reason for admission is aggression, and the use of Mental Health Act detentions and Community Treatment Orders.

With the trend towards increased prescribing of neuroleptic medications, a level of increased violence can be anticipated for the future.

There is the possibility of ameliorating the presence of violence in the severely mentally ill by ensuring pharmacogenetics is more fully recognised as a significant factor, and that genotype testing is adopted in order to assess the ability of the individual to metabolise neuroleptic medication.

‘Mental disorders are neither necessary nor sufficient causes of violence’.

Source: Heather Stuart (2003) [Violence and mental illness: an overview](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1525086/)
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1525086/>

Useful websites:

Law Project for Psychiatric Rights:

<http://psychrights.org/index.htm>

AHRP Alliance for Human Research Protection

www.ahrp.org

MindFreedom International: 26 Years of Human Rights Activism in Mental Health

<http://www.mindfreedom.org/>

The Center for the Study of Empathic Therapy, Education and Living.

<http://www.empathictherapy.org/>

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August 2012