Neuroleptic Physical

Adverse Drug Reactions

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Neuroleptics and Antipsychotics

The terms ‘antipsychotic’ and ‘neuroleptic’ are used interchangeably in research papers, although in clinical guidelines and practice, ‘antipsychotic’ is the most frequently used.

Prior to these terms these medications were known as ‘Major Tranquillisers’. The term ‘neuroleptic’ was accepted in 1955 and eventually became known as ‘antipsychotic’ by drug companies who used it as a marketing ploy to influence doctors and patients to believe that the drug’s specific action was to treat and prevent psychosis. However this ploy puts considerable distance from numerous other ‘antipsychotic’ actions and the hard reality of what the drug does to the brain.

Neuroleptic literally means to ‘seize the nerve’, a chilling scenario. For this reason, throughout this document the word ‘Neuroleptic’ will be used in place of ‘Antipsychotic.’

Neuroleptic Adverse Drug Reactions and Pharmacogenetics

Neuroleptic ADR are caused by the way the drugs act on neurons and neurotransmitters in the brain and body and are therefore **IATROGENIC.** i.e. neuroleptic induced.

ADR are influenced by the genetically predetermined rate of metabolism known as **Pharmacogenetics.** When people have the in-born slower rates of metabolism i.e. **Poor Metaboliser** or an **Intermediate Metaboliser Genotype** profiles, neuro-toxicity increases which is associated with the severity of ADR. [1, 2]

All people who take neuroleptics will be affected by various ADRs, either within a short or longer period of time.

60% of patients experience severe/very severe side effects.[3]

Adverse Drug Reactions and Side Effects

In both patient and professional literature, to explain the ‘undesired effects of medication’, pharmaceutical companies commonly use the term ‘side effects’. Because the term both minimises and obscures the cause of ‘side effects’, the term is replaced by Adverse Drug Reactions (ADRs) in this document.

Many neuroleptic physical ADRs are not found in mainstream literature. In order to readdress this situation, this document provides up to date and concise ADR information for mental health and social care practitioners.

Neuroleptics and Neurotransmitters

It is well known that neuroleptic medication depletes dopamine by disrupting the dopamine neurotransmitters in the brain.

What is not so well known is that atypical neuroleptic medication disrupts other neurotransmitters such as serotonin, adrenaline, noradrenaline and acetylcholine, that play an important role in the maintenance of all body systems.

It is the balance between all of the neurotransmitters that is important and this balance is in constant flux to maintain long term stability. If the level of one neurotransmitter is artificially raised or lowered by medication, all other neurotransmitters are relatively affected and stability is lost.

Unnatural interference with neurotransmitters by neuroleptics causes deterioration of physical health and leads to various iatrogenic illnesses.

Physical Functions of Dopamine

Dopamine as a **neurotransmitter:**

- Co-ordination of voluntary and involuntary movements and muscular strength.
- Participates in thermoregulation and regulates metabolism.
- Enables the natural regulation of fat and sugar, sleep patterns, control of hunger, thirst, fatigue, and circadian cycles.

Dopamine as an endocrine **neurohormone:**

- Participates in the regulation of blood pressure, heart rate, cardiac output, fluid and sodium balance, gastric motility, lactation, fertility, and bone strength.[4]
- Enables the flight and fight responses in the face of danger.[5]

Introduction to Body Movement Disorders

The Extra Pyramidal System in the brain controls normal body movements with dopamine playing an important role. Neuroleptics reduce dopamine causing excessive abnormal body movements.

Neuroleptic Induced Extra Pyramidal Symptoms (EPS):

- **Tardive Dyskinesia**
- **Parkinsonism**
- **Tardive Dystonia**
- **Oculogyric Crisis**
- **Akathesia**

These iatrogenic conditions result from adverse structural brain changes.[6,7 & 8]

Adverse neuroleptic reactions can be due to people's inability to metabolise psychiatric medication when they have Poor Metaboliser Genotype Enzymes.[1]

Tardive Dyskinesia (TD)

In 1959 TD was first reported to be linked to neuroleptics.[9]

TD is due to neuroleptic induced Target Organ Toxicity causing irreversible damage to the brain cells. TD can appear within 6 months, is caused by both typical and atypical drugs and the risk increases with chronic long-term exposure.[10, 11, 12]

Memory impairment is associated with patients with high TD scores.[13]

5-HT2C serotonin receptor gene variants are associated with Tardive Dyskinesia, depending on age, duration of treatment, dose and sex.[14]

Tardive Dyskinesia (TD)

TD symptoms are disfiguring and include:

- Chewing movements of lower jaw.
- Lip sucking and smacking.
- Blowing in and out and bulging of cheeks.
- Facial grimacing.
- Abnormal tongue movements i.e. the tongue quivers – protrudes.
- Finger movements as though an invisible guitar is played.
- Rocking and swaying of the body.

Body actions are involuntary, potentially irreversible and there is no proven treatment.

Less Well Known Tardive Dyskinesia Symptoms

There are many other "lesser" appreciated symptoms of TD:

- Restless legs (especially at night)
- Poor sleep
- Loss of gag reflex/swallow – can lead to pneumonia
- Unstable blood pressure and heart rate due to autonomic dysfunction.
- Pain syndrome i.e. tardive pain
- Depression.
- Psychosis as the condition progresses.
- Dementia

All the above ‘lesser known symptoms’ are all possible (if not likely) in Tardive syndromes, largely because of neuroleptic drug treatments, and will be found if doctors take the time to "think" and ask questions carefully.
(G. E. Jackson MD, Personal Communication)

Parkinsonism

Neuroleptic Induced Extra Pyramidal Symptoms (EPS) manifest in the same way as they do in Parkinson's Disease:

- Tremor, ranging from being almost imperceptible to incessant shaking.
- Hypersalivation: excessive salivation
- Bradykinesia: slowing down of large muscle movement
- Shuffling gait
- Reduced emotional expression
- Rigid stiff muscles

When anti-cholinergic medications are prescribed to alleviate EPS, patients are then exposed to additional ADRs.

Anti-Cholinergic Adverse Drug Reactions

The role of the Peripheral Nervous System is to connect the Central Nervous System (brain & spinal cord) to the limbs and organs.

Anticholinergic medications disrupt the **Peripheral Nervous System** causing the following ADRs:

- Blurred vision
- Dry eyes
- Dry mouth
- Increased heart rate
- Nausea & vomiting[16]
- Urine retention and Bladder distension
- Constipation
- Headaches
- Nasal congestion[15]

Anticholinergic (antimuscarinic) medications increase brain damage associated with cognitive impairment and worsen Tardive Dyskinesia.[16, 17]

Tardive Dystonia

Dystonia is characterised by involuntary twisting and repetitive movements, or abnormal postures[18, 19, 20] due to dysfunction or over-activity, in the brain structures that control movement.

These sustained and disfiguring painful muscle spasms include:

- Torticollis - head and neck are twisted to one side
- Retrocollis - head and neck are pulled back between the shoulder blades
- Blepharospasm - eyelids are forcefully squeezed shut.
- Excessive arching of the back.

Oculogyric Crisis

Oculogyric Crisis is an acute dystonic reaction to certain drugs including neuroleptics, such as Olanzapine,[21, 22] Risperidone, [23] Amisulpiride[24] and Clozapine.[25]

In addition to the acute presentation, it can develop as a recurrent syndrome.[26, 27, 28]

Characteristics include rotating of the eyeballs with extreme and sustained upward deviation accompanied by ocular pain. The eyes may converge, deviate upward and laterally, or downward.[27, 28]

Associated Dystonic Symptoms with Oculogyric Crisis

Some of these are similar to the symptoms described in Tardive Dyskinesia, Parkinsonism and Tardive Dystonia as there is a degree of overlap.

Blepharospasm	Respiratory dyskinesia
Periorbital twitches	Backwards and lateral flexion of neck
Protracted staring episodes	Widely opened mouth
Eye blinking	Tongue protrusion
Lacrimation	Intensely painful jaw spasm which may result in breaking a tooth
Drooling	

Refs 27, 28

Associated Psychiatric Symptoms with Oculogyric Crisis

The clinical spectrum of Oculogyric Crisis is poorly understood, leading to the frequent mislabel of a psychogenic disorder.[27]

Vertigo	Paranoia	Mutism
Anxiety	Depression	Palilalia
Agitation	Recurrent fixed ideas	Violence
Compulsive thinking	Depersonalization	Obscene language

Refs 27, 28

"A wave of exhaustion follows some episodes. The abrupt termination of the psychiatric symptoms at the conclusion of the crisis is most striking."[27, 28, 29]

Other Symptoms Associated with Oculogyric Crisis

Increased blood pressure & heart rate	Facial flushing
Pupil dilation	Headache

Refs 27, 28

Akathesia

Neuroleptic induced symptoms of Akathesia are characterized by unpleasant sensations of inner restlessness that manifest with a physical inability to sit still or to remain motionless.

Patients have described the feeling as a sense of inner tension and torment.

Because of the severe negative psychological effects associated akathesia, it is described in greater detail in:

‘Neuroleptic Psychological Adverse Reactions’[30]

Conclusion to Body Movement Disorders

- **Tardive Dyskinesia**
- **Tardive Dystonia**
- **Oculgyric Crisis**
- **Akathesia**
- **Extra Pyramidal Symptoms**

- are frequent combinations that make patients look ‘odd’, making them extremely vulnerable in the public environment.

Abnormal body moments such as TD present an obvious stigma of 'madness' and constitute a severe social handicap ... by causing embarrassment to the family and friends and apprehension on the part of the potential employers.[31]

Endocrine Disorders Caused by Neuroleptic Dopamine Disruption

- **Metabolic Syndrome**
- **Sexual Dysfunctions**
- **Osteoporosis**
- **Thyroid Disorders**

These conditions have a follow on effect causing:

- **Cerebro Vascular and Cardiac Disease**

“Metabolic Syndrome”

Symptoms:

- Cortisolaemia i.e. obesity with excessive abdominal fat
- Diabetes type-2
- Hyperlipidemia i.e. Lipid abnormalities or High Cholesterol
- Hypertension or High Blood Pressure
- Insulin resistant Diabetes.[32]

Some neuroleptics interfere with appetite regulation networks in the brain resulting in excessive appetite and massive weight gain associated with diabetes and heart disease.[33]

5-HTT (serotonin transporter) and 5-HT2A (serotonin receptor) gene variants are associated with obesity and tryptophan hydroxylase 2, (TPH2) gene variants are found to be associated with diabetes.[14]

The occurrence of metabolic syndrome with typical *and* atypical neuroleptics is 2-4 times higher than in people who are not prescribed neuroleptics.[34]

Sexual Dysfunction Male and Female

Dopamine as a neurohormone acts as a natural brake by inhibiting excess production of prolactin hormone that is involved in normal sexual functions i.e. lactation and sexual gratification.[35]

Dopamine depletion by neuroleptics removes the brake causing high levels of prolactin hormone, a condition known as Hyperprolactemia. This condition creates many sexual dysfunctions.[36, 37, 38]

Sexual Dysfunction Male and Female

Symptoms of Hyperprolactemia:

MALE	FEMALE
Gynecomastia: enlarged breast tissue	Galactorrhoea: production and secretion of breast milk
Galactorrhoea: production and secretion of breast milk	Amenorrhoea: irregular or absent menstruation
Retrograde Ejaculation	Loss of Libido
Loss of Libido	Anorgasmia
Sterility or damaged sperm DNA	Infertility
Erectile dysfunction	Birth defects due to damaged DNA/sperm
Testicular atrophy	

Refs 36, 37, 38

Osteoporosis

Osteoporosis is associated with neuroleptic induced Hyperprolactemia.[39, 40]

Osteoporosis aetiology:

- Long term prolactin-raising neuroleptics pose a high risk of bone density reduction[36]
- Reduced bone density in neurolepticized males[39]
- Risk factor for osteoporosis in young women[40]

Osteoporosis symptoms:

- Bone pain
- Vulnerability to fractures

Neuroleptic Disruption of Thyroid Production

The thyroid is an endocrine organ and it's function will inevitably be disrupted in both the short and long term by neuroleptic drugs in a similar way to other endocrine disorders caused by neuroleptic interference.

Limited research indicates thyroid dysfunction is relatively common in patients with schizophrenia[41] and long-term neuroleptic treatment can induce thyroid autoimmunity associated with hyperprolactinaemia.[38] Serum levels of T_4 (Thyroxine) have been found to decline after treatment with neuroleptics, and other psychiatric drugs.[42]

Both *Hyper*thyroidism and *Hypo*thyroidism can mimic psychiatric symptoms which may lead to misdiagnosis with the potential to incur neuroleptic prescribing.

Cerebro-Vascular Disease

The neuroleptic impact on the endocrine system increases the risk of microvascular and macrovascular disease,[8] causing the following cerbro-vascular conditions.

Symptoms:

- Hyperlipidemia (High Cholesterol)
- Cerebral Vascular Accidents i.e. Stroke
- Cardiac Rhythm abnormalities
- Heart Failure
- Myocardial Infarction (heart attack)
- Cardiac Death[43]
- Deep Vein Thrombosis
- Pulmonary Embolus - potentially fatal
- Vascular Dementia

Neuroleptic Cardiotoxicity

Animal studies have demonstrated the cardiotoxic effects of neuroleptic drugs.[44]

Neuroleptic drug resulted in cardiac lesions of variable magnitude in animals, with changes that include thickening of blood vessels, damage to cardiac muscle fibres, such as disintegration, swelling, fibrotic scarring[45] and cell death (necrosis).[46]

Based on their discoveries, the authors recommended that patients receive an ECG (electrocardiogram) and cardiac ultrasound (echocardiogram) PRIOR to beginning any antipsychotic drug therapy.[46]

These tests will not prevent the development of neuroleptic cardiotoxicity.

Neuroleptic Malignant Syndrome (NMS)

This condition is similar to a viral infection of the brain i.e. Encephalitis.

NMS results from the dysregulation of the sympathetic nervous system[47] which is part of the autonomic nervous system, and is vital for the stability of life functions.

NMS is associated with:

- All neuroleptics, typical and atypical.[48, 49]
- Rapid and large increases in neuroleptic dose
- Conjunction with other neuroleptics (polypharmacy).

Neuroleptic Malignant Syndrome (NMS)

Clinical Symptoms of NMS:

Hyperpyrexia	Generalised muscle rigidity
Altered mental status	Sweating
Hypertension	Seizures
Hypotension	Cardiac arrhythmia
Tachycardia	Renal failure
Tremor	Respiratory failure
Incontinence	Sialorrhea (drooling)
Muscle weakness	Dysarthria (speech difficulty)

Mortality rates for NMS, once reported at 20-30% are now estimated at 5-11.6%. Incidence is probably less now than in the past because of increased awareness of NMS and efforts at prevention.[49]

Temperature Dysregulation

Neuroleptics disable thermoregulatory mechanisms[50] causing temperature dysregulation i.e. **Hypothermia and Hyperthermia.**

Neuroleptics most commonly cause ***hyper***thermia[51] although they can also cause ***hypo***thermia. This highlights the complexity of the temperature regulation system.[48]

The disruption of normal acetylcholine transmission by neuroleptics causes **Hyperthermia** i.e. reduced sweating.

During heat waves, neuroleptic medications increase patients' risk of death from heat stroke, **two fold** compared to the general population.[52]

Respiratory Disease

Dopamine plays a key role in the regulation of the brain's respiratory/breathing centre and clearance of excess lung mucous. OK

Neuroleptic dopamine depletion causes:

- Respiratory Dyskinesia - difficulty in breathing.[53]
- Respiratory Arrest
- Impaired clearance of excessive lung mucous.[4]
- Impaired recovery from pulmonary oedema due to cardiac disease.[4]
- Choking and aspiration.[53]
- Excess mortality among in-patients.[54]
- Deaths from respiratory disorders gave rise to the highest relative risk after accidental deaths.[54]

Agranolocytosis

Clozapine can cause Agranulocytosis which is a blood disorder in which the total white blood cell (WBC) count falls to a dangerous level. Blood tests are taken prior to initial prescribing to ascertain the WBC is normal.

In order to prevent fatalities from Agranulocytosis, mandatory blood tests are taken through out Clozapine prescribing at various time intervals. WBC can drop spontaneously or due to bacterial infections; patients have to stop Clozapine immediately, causing emergency hospital admission and change of neuroleptic medication. Specific antibiotic medications have to be used as some antibiotics further decrease one type of WBC.

Blood monitoring may prevent neurolepticised people from dying from agranulocytosis, but it does not prevent iatrogenic blood dyscrasia.

Clozapine has been linked to 950 deaths since being licensed in 1990 — equivalent to nearly one fatality a week.[55]

Neuro-degenerative Brain Changes

The book **“Drug induced Dementia: A Perfect Crime”** presents a methodical analysis of the scientific and epidemiological evidence which confirms psychopharmaceuticals as a cause of brain damage and premature death.[8]

The Jellinger Study, 1977. Human Autopsies[56]
46% of patients exposed to neuroleptics displayed prominent injury to the caudate nucleus, compared with 4% of psychotic patients who had avoided neuroleptic drugs. The caudate nucleus plays a key role in the modulation of movement, cognition, and mood.

The brain cell changes showed the brain’s response to chemical injury; cell death (necrosis), disintegration and inflammation, also found in systemic lupus patients and Parkinson’s Disease.[8]

Neuroleptics and Progressive Brain Damage

There are 25 medical articles on brain damage associated with neuroleptic drug treatment compiled by the late psychiatrist Loren Mosher, MD.[57]

Researchers in Denmark found a dose dependent association with brain shrinkage, estimating the risk of atrophy to be 6.4% for each additional 10 grams of chlorpromazine, or other neuroleptic in terms of equivalent dose.[7, 8]

Brain Damage Associated with Poor Outcomes

Neuroimaging Studies of Humans:

Following one year of neuroleptic therapy, patients demonstrated an 8% increase in lateral ventricle volume, a 1% reduction in total brain volume, and a 3% reduction in whole brain grey matter.

These brain changes were significant statistically, being clinically related to poor outcomes in terms of psychotic symptoms, physical health, social intimacy, and independence. The grey matter changes corresponded to cumulative neuroleptic dose.[8, 30, 58]

Additional Neuroleptic Iatrogenic Adverse Reactions

Liver malfunction:

Atypical antipsychotics commonly cause symptomless increase in aminotransferase liver enzyme levels. Elevated transaminases, which can be an indicator of liver damage[59] have been reported with olanzapine.[60]

Kidney failure:

Acute renal failure induced by neuroleptics.[61]

Constipation:

Bowel obstructions.[62, 63]

Additional Neuroleptic Iatrogenic Adverse Reactions

Muscular Weakness:

Loss of muscle power is associated with high neuroleptic dose, in conjunction with polypharmacy and NMS.[64]

Sunburn:

Photosensitivity occurs with atypical neuroleptics, i.e. Amisulpride[65] and Clozapine.[66] Patients are more prone to increased Sun Sensitivity when polypharmacy is practised.

Ocular Changes:

Cataracts can occur with Neuroleptics.[67]

Sudden ‘Unexplained’ Deaths

Many reports are available of sudden deaths of patients who were medicated with high dosages of neuroleptics. [68, 69,70]

Cardiovascular causes of death are most common, accounting for the majority of sudden and unexpected deaths, thought to result from fatal arrhythmias. Some neuroleptics prolong the cardiac QTC interval even at therapeutic doses.[71]

The risk of sudden cardiac death is elevated at low doses, even among patients who receive neuroleptic drugs for non-schizophrenic conditions.[4, 72]

Sudden ‘Unexplained’ Deaths cont…

- The death of Orville Blackwood in 1991 from heart failure, resulted from being injected with a cocktail of Promazine and Fluphenazine.[73]
- In 1990, there were thirteen sudden deaths of patients who were medicated with Pimozide in the UK.[74]
- 20 people died whilst taking Olanzapine out of 2,500.[75]
- In 2009 sudden unexplained deaths of psychiatric in-patients were at an eight year high.[76]

In England the increase in rates of Sudden Unexplained Deaths is significant. 8.8% per year overall, 7.6% in men and 10.4% in women.[77]

"We know therefore that the mortality rate among people who are in contact with specialist mental health services is nearly four times that for the general population.”[78]

As more people are diagnosed and treated with neuroleptics, the number of patient mortalities has increased.[79]

Conditions Contributing to Premature Death

"When key regions of the brain are destroyed, numerous life-sustaining functions are affected." *(G. E. Jackson M. D. Personal Communication)*

Metabolic Syndrome	Hyperthermia – Heat Stroke
Hyperprolactemia	Hypothermia
Cardiac Conditions	Kidney Failure
NMS	Bowel Obstruction
Parkinsonism	Cerebro-vascular disease
Respiratory conditions	Tardive Dyskinesia & Dystonia

All these conditions leading to premature death result from unnatural medication interference with the natural life-sustaining functions of the brain.

Premature Death, Parkinsonism and Tardive Conditions

"Parkinson's disease and Tardive Dyskinesia (TD) both contribute to premature death. The reason for this is that both conditions reflect brain damage." *(Source G. E. Jackson M. D. Personal Communication)*

In a cohort of 608 Asian patients diagnosed with schizophrenia…,
Risk of death was 2.6 times higher among those with TD.[80]

Sample of 200 patients receiving neuroleptics was assessed in 1995.
Deceased patients had higher average scores for Parkinson syndrome than those who survived.[81]

10-year mortality rate among patients with TD.
TD was significantly associated with increase in mortality.[82]

41% of TD patients died within 10 years vs. 20% of those without TD.[83]

Tardive Tourettism

Tardive Tourettism has the same symptoms of Tourette's Syndrome and is caused by neuroleptics.[84, 85]

Tourette's syndrome includes physical and vocal tics, which can either be both simple and complex.

Physical tics include jerking the head, teeth grinding, rolling eyes and jumping up and down.

Vocal tics include blowing, squeaking, sniffing, swearing, verbalising involuntary obscene thoughts, repeating other people's phrases and inappropriate language with sexual connotations.[86, 87]

Tourette's poses social difficulties and includes low self-esteem, embarrassment and becoming isolated socially.

Conclusion

The physical Adverse Reactions of neuroleptic medication may be described as ‘side effects’, but in fact are the *main control* effects of these medications acting on the Central Nervous System.

In general medicine, when severe iatrogenic adverse reactions are caused by common medications, then the ‘offending’ medication is scrutinised and banned.

However this sanction does not happen within psychiatry. Neuroleptic adverse reactions are either treated with common medications, - which patients may or may not be able to break down efficiently, depending on their genotype profile - dismissed, ignored, or often seen as part of the psychiatric illness resulting in treatment with further psychiatric medications. On occasion surgery to rectify the adverse reaction is performed.

Ethics

Some UK Key Opinion Leaders are insistent that not all neuroleptic ‘side effects’ should be revealed to patients, for fear they may not want to take neuroleptic medication.

This attitude and practice poses serious ethical questions. The deliberate hiding of ‘side effects’ information from patients, carers and professionals is blatant deception and is misleading and disrespectful. The result is that many people are being coerced into thinking neuroleptics are safe medications. Nothing could be further from the truth.

Neuroleptic medications compromise and slowly impoverish peoples’ lives, how their bodies function, their dignity and self respect. None of this is conducive to social inclusion or the potential of a full recovery.

Successful Non – Neuroleptic Treatment

There is alternative successful treatment without the use of neuroleptic medications. This rich and sadly suppressed history of humanistic alternative treatment has been shown consistently to present outcomes far superior to those of treatment with neuroleptic medications.

Successful Non-Neuroleptic Treatments for “Schizophrenia” [88]

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