Antidepressant
SSRI
Physical
Adverse Drug Reactions
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Preface

In the UK, NICE guidelines recommend Serotonin Selective Reuptake Inhibitor (SSRI) antidepressants as the treatment of choice for all types of depression.\(^1\) Antidepressant medications are also prescribed for other common mental health disorders such as obsessive compulsive disorder, general anxiety disorder, panic disorder, social phobia and agoraphobia.\(^2\)

Despite the introduction of Improving Access to Psychological Therapies (IAPT), prescription rates for antidepressant medications have risen from 36 million prescriptions in 2008 to 46.7 million in 2011.\(^3\)
Preface

In current UK mainstream literature reporting and availability of SSRI physical Adverse Drug Reactions (ADR) is varied and limited. The better-known common physical SSRI ADRs are available whilst unfamiliar ADRs are not reported.

Drug company trials last for a short term period of 6-8 weeks; SSRI drug monograms report ADRs experienced in that time period, even though SSRI treatment is far longer. Consequently ADRs resulting from SSRI long-term use due to allostatic load is not addressed in mainstream literature.
Preface

The issues of allostatic load and long term use of SSRIs probably accounts for ADR discrepancies i.e. weight loss being a frequent ADR, which contrasts with weight gain, which is infrequent.\textsuperscript{4} Drug companies do not explain the reason for the discrepancies.

Mainstream literature does not address patients’ susceptibility or intolerance due to genetic differences of breaking down medications, otherwise known as pharmacogenetics, that is the cause of ADRs.

In order to address these deficits, this document provides extensive referenced SSRI medication ADR information thereby promoting increased awareness for mental health and social care practitioners.
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”.

This term both minimises and obscures the cause of “side effects” which are in reality Adverse Drug Reactions to drug toxicities and are dose related.\(^1\)

SSRI antidepressant ADR are caused by the way the drugs act on neurons and neurotransmitters in the brain and body and are therefore iatrogenic. i.e. induced by medications.

Unnatural interference with neurotransmitters by SSRIs causes ADRs which range from being unpleasant to life threatening.
Neurotransmitters

SSRIs affect the serotonin neurotransmitter by binding to the Serotonin Reuptake Transporter. What is less well known is that SSRIs indirectly influence other neurotransmitters and receptors in the brain such as dopamine, histamine, adrenaline, noradrenaline and acetylcholine.

Neurotransmitters play important roles in the health of all body systems and the maintenance of long-term health stability (homeostasis) depends on the balance of all the neurotransmitters, which are constantly readjusting in order to maintain stability in a changing environment.

If the level of one neurotransmitter is artificially raised or lowered by medication, all other neurotransmitters are relatively affected, stability is lost and health deteriorates.
Neurotransmitters

Short-term effects of SSRIs cause an initial increase of serotonin in the synapse, followed by a decrease due to the regulatory feedback mechanism. Subsequent increase of serotonin occurs several weeks later.\(^5\)

Long-term antidepressant treatment results in the reduction or depletion of brain chemicals i.e. serotonin and norepinephrine. This fact is supported consistently by many studies with animals subjected to SSRI drugs.\(^5\)

Persistent SSRI treatment causes "changes in receptor density, changes in receptor sensitivity, and changes in the cellular processes which control neurochemical synthesis and release. ...chemical therapies alter gene expression and re-wire brain circuits in ways that can result in delayed or persistent harm"\(^7\)
Pharmacogenetics

Adverse Drug Reactions are influenced by the genetically predetermined rate of metabolism known as **Pharmacogenetics**. When people have inborn slower metabolising rates and / or variations in drug transporters, the accumulation of neuro-toxicities results in adverse reactions.

Antidepressant metabolism is complex and growing information indicates the link between the Serotonin Transporter Gene (SERT) and clinical effects of SSRIs. Other drug metabolising enzymes such as CYP450 pathways play an important role in SSRI responses.
Pharmacogenetics

“Genetic factors contribute for about 50% of the AD (antidepressant) response.” 11 Hyponatraemia, a metabolic clinical effect/adverse reaction induced by SSRIs, is more likely to occur when people have decreased metabolism via CYP450 2D6. 12

Patients who experience ADR are recorded as having ‘intolerance’ or ‘susceptibility’ to medication. Due to pharmacogenetic training deficits, the majority of doctors remain unaware of the underlying pharmacogenetic genetic ‘susceptibility’ cause for ADR.

Drug-drug interactions, when one drug inhibits/induces a metabolising pathway necessary for the efficient metabolisation of another drug, can increase drug toxicities causing ADRs.
Allostatic Load

Allostasis refers to the “…adaptations made by the human organism in response to internal and external demands.” e.g. the stress response in the face of perceived danger – raised cortisol levels.

Allostatic load refers to the point where such adaptations become maladaptive i.e. become prolonged, overactive or underactive.

All foreign chemicals, such as psychotropic drugs act as environmental stressors to the body’s systems and thereby create allostatic load.
Allostatic Load

There are 4 types of Allostatic Load:

1. Repeated Responses to Repeated Hits
Repeated exposure to SSRIs i.e. repeated dosing, causes structural changes; swelling and kinking in serotonin nerve fibres have been found in animal studies. In response to SSRI drug induced injury the brain produces growth factors to repair the damaged neurons called the allostatic response.
Allostatic Load

2. Lack of Adaptation
Some patients can get accustomed to the physiological reactions of SSRIs, while others do not adapt and SSRIs trigger persistently raised hormone levels such as prolactin. Another example is suppression of REM sleep with many SSRIs.

Some patients become sensitised i.e. have a heightened response, especially Poor Metabolisers and those with other pharmacogenetic variations for metabolising SSRIs.

Others become physically dependant on SSRIs, with a reduced therapeutic effect and the consequent need for dose increase, known as tolerance. Tolerance incurs withdrawal symptoms on cessation when SSRIs are taken long term.⁵
Allostatic Load

3. Prolonged Response
Prolonged maladaptive responses after medication discontinuation can cause withdrawal or rebound phenomena. Variability in the individual’s ability to metabolise a drug can alter the response and withdrawal symptoms can last for weeks or months. ¹³


4. Inadequate response
SSRIs dampen the stress response i.e. reduce the release of cortisol under stress thereby removing the body’s ability to repair damage arising from any other stress.

“…cortisol and other chemicals may surge or dip to levels which are potentially more harmful than those which existed prior to drug therapy” ⁵
Endocrine and Metabolic Disorders

- Cortisolaemia
- Diabetes
- SIADH Syndrome of Inappropriate Antidiuretic Hormone Secretion:
  - Hyponatraemia
- Hyperprolactinaemia:
  - Sexual Dysfunctions
  - Osteoporosis
  - Breast Cancer
  - Cardiac Disease
- Thyroid Disorders
Cortisolaemia

Cortisolaemia symptoms include obesity, excess abdominal fat and fluid retention or oedema.

SSRI antidepressants in the short-term have been shown to raise the levels of cortisol\(^\text{14}\) a stress hormone. Continuous exposure to SSRIs has been proposed for the return of high levels of cortisol and ACTH, a pituitary hormone that stimulates the secretion of cortisone from the adrenals.\(^\text{5}\)

Physical effects of raised cortisol are weight gain, immune dysfunction and atrophy of the hippocampus with memory loss.\(^\text{5}\)

Long term raised cortisol causes insulin resistance,\(^\text{15}\) which precedes diabetes.
Diabetes

Insulin resistant diabetes is due to insulin deficiency and classified as Diabetes Mellitus Type 2. Symptoms include excessive thirst, frequent urination, constant hunger, feeling tired, loss of weight and muscle bulk, constipation, blurred vision, thrush, skin infections and cramps.\(^{16}\)

All types of antidepressants including SSRIs and tricyclic, increase type 2 diabetes risk,\(^{17}\) and a large Finnish study found the risk was doubled.\(^{18, 19}\)

People over the age of thirty are especially prone to an increased risk of diabetes, when SSRIs are taken long term.\(^{20}\)

Animal research has implicated SSRIs as inhibitors of insulin signalling and potential inducers of cellular insulin resistance.\(^{21}\)
Syndrome of Inappropriate Antidiuretic Hormone Secretion

SIADH induced by SSRI antidepressants\textsuperscript{22,23} is a condition due to excessive release of anti-diuretic hormone, resulting in an electrolyte imbalance of sodium, causing the following symptoms:

- Hyponatraemia
- Delerium
- Myoclonus
- Hyporeflexia
- Tremor/asterixis
- Headache
- Nervousness
- Ataxia – incordination
- Dysarthria - speech difficulty
- Abnormal respiration
- Seizures
- Coma
- Lethargy
- Insomnia

Ref: 22, 24
Hyponatraemia

Hyponatraemia is a potentially serious metabolic condition in which there is insufficient sodium in the body fluids outside the cells. Fluid moves into the cells causing them to swell. The body cells can tolerate some oedema but the brain cells, being encased in a rigid skull, cannot.

Hyponatraemia is associated with CYP450 2D6 diminished variant genotype\(^ {12}\) and causes the following symptoms:

- Nausea and Vomiting
- Headache
- Confusion
- Lethargy
- Fatigue
- Delayed reaction time
- Mental errors
- Restlessness and Irritability
- Muscle weakness
- Muscle spasms or cramps
- Appetite loss
- Seizures
- Instability
- Decreased consciousness
- Coma
- Death

Refs: 12, 28
Hyperprolacinaemia

The serotonin neurotransmitter is one of the primary chemicals with a stimulatory effect upon the prolactin hormone and plays various roles in reproduction, fertility and sexual functions.

Hyperprolacinaemia, an excess of prolactin, is caused by SSRI’s disruption to the endocrine system. In a French pharmacovigilance database study, 17% of drug induced hyperprolacinaemia cases had been induced by SSRIs.

Hyperprolacinaemia has physical consequences of various sexual dysfunctions in men and women.
Sexual Dysfunction and Malfunction Male and Female

Sexual dysfunction is the most common SSRI ADR. 60% of patients can experience delayed ejaculation, anorgasmia, and decreased libido.\textsuperscript{33, 34} Sexual dysfunction effects continue as long as the drug is taken\textsuperscript{6} and may persist after the drug is withdrawn and continue indefinitely.\textsuperscript{20}

**Symptoms include:**

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>Decreased libido</td>
<td>Decreased libido</td>
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<tr>
<td>Erectile dysfunction</td>
<td>Lactation - Galactorrhoea</td>
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<tr>
<td>Gynecomastia: breast enlargement</td>
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<td>Hypogonadism: testicular atrophy</td>
<td>Amenorrhoea: absent menstruation</td>
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<tr>
<td>Priapism – persistent erection</td>
<td>Anovulation</td>
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<tr>
<td>Infertility</td>
<td>Delayed orgasm &amp; anorgasmia</td>
</tr>
<tr>
<td>Milk secretion – Galactorrhoea</td>
<td>Infertility</td>
</tr>
</tbody>
</table>

Refs: 5, 6, 20, 32, 33 - 35.
**Delayed Lactation in New Mothers**

SSRIs are linked with delayed lactation in new mothers; because these medications are serotonergic they disrupt serotonin balance and thereby cause dysregulation of lactation.\(^{36}\)

For other pregnancy related, neo-natal and fetal adverse effects of SSRIs see pages 52 – 58.
Osteoporosis

Osteoporosis, also known as Bone Mineral Density (BMD) loss, is a physical consequence of chronic long-term SSRI use related with hyperprolactinaemia.\textsuperscript{32, 37, 38}

Osteopenia is a term used to describe lowered BMD and considered a precursor to osteoporosis.\textsuperscript{39} Serotonin disruption in mice research induces osteopenia, which correlates with men who take SSRIs having lowered BMD compared with non users.\textsuperscript{40}

SSRIs are linked with greater susceptibility to bone fractures\textsuperscript{41} and the risk may be increased with higher doses.\textsuperscript{42}
Osteoporosis

Women taking anti-depressants have a 30 percent higher risk of spinal fracture and a 20 percent high risk for all other fractures\textsuperscript{43} and SSRI use in adults aged 50 and older is associated with a 2-fold increased risk of clinical fragility fracture.\textsuperscript{44}

Prolonged SSRI use causes a significant risk of non-vertebral fractures\textsuperscript{45} such as hip fractures in the elderly.\textsuperscript{46}

Osteoporosis signs and symptoms:

- Bone pain
- Fragile bones with vulnerability to fractures
Breast Cancer

Hyperprolactinaemia in pre and post-menopausal women is associated with the risk of developing breast cancer.\textsuperscript{47, 48}

“Prolactin hormone functions to stimulate the growth and motility of human breast cancer cells.”\textsuperscript{49} and is confirmed by research in rats which depicts carcinogenesis of the male mammary gland following an induced secretion of pituitary prolactin.\textsuperscript{50}

When SSRIs are taken for 36 months or longer there is an increased risk of breast cancer although the association of hyperprolactinaemia and SSRIs is not yet clear.\textsuperscript{32}
Cardiac Disease

Hyperprolactinaemia presented in 25% of patients prescribed SSRIs with heart failure\textsuperscript{51} and another study has proposed hyperprolactemia might induce or maintain cardiac disease in some patients.\textsuperscript{52}

SSRIs can cause death due to cardiac arrest,\textsuperscript{53} and may cause sudden cardiac death in women.\textsuperscript{54} Abnormal changes in the electrical activity of the heart\textsuperscript{55} such as ventricular arrhythmias\textsuperscript{56,57} are associated with an increased risk of myocardial infarction.\textsuperscript{58}
Cardiac Disease

Patients on SSRIs before Coronary Artery Bypass Grafting (CABG) had “a higher prevalence of diabetes, hyper-cholesterolemia, hypertension, cerebrovascular disease, peripheral vascular disease, and previous cardiovascular intervention" and had an increased risk of mortality post CABG surgery.\(^{59}\)

Drugs with serotonergic activity cause heart artery spasms, which could link SSRI serotonergic activity with myocardial infarction\(^{60}\) and serotonin may contribute to the development and progression of cardiac valve disease.\(^{61}\)

Cardiovascular toxicity is associated with CYP450 2D6 diminished variant genotype.\(^{62}\)
Thyroid Disorders

Hyperthyroidism and Hypothyroidism are both endocrine disorders classed as adverse events of SSRIs.\(^4\)

Clinical signs and signs and symptoms of SSRI - induced hypothyroidism may be asymptomatic.\(^63\)
Serotonin Syndrome

Serotonin Syndrome is an iatrogenic, potentially life threatening condition due to excessive serotonin levels in the brainstem and spinal cord, incurred by SSRIs causing serotonin toxicity. Precipitating factors for Serotonin Syndrome:

- The consecutive use of SSRIs.
- Raising SSRI dose.
- Prescribing of two serotonergic drugs simultaneously.
- SSRI with either MAOIs, tryptophan or lithium.
- Abrupt withdrawal of antidepressants.
- CYP450 diminished drug elimination variant genotype, Intermediate CYP 2D6 and Poor CYP 450 Metabolisers.
Serotonin Syndrome

There is a triad of clinical symptoms\textsuperscript{64, 74} which range from being barely perceptible to fatal.\textsuperscript{64}

<table>
<thead>
<tr>
<th>Neuromuscular Effects</th>
<th>Autonomic Effects</th>
<th>Mental Status Changes</th>
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<tbody>
<tr>
<td>Ataxia – loss of co-ordination</td>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td>Hyperreflexia – heightened reflexes</td>
<td>Labile blood pressure</td>
<td>Confusion</td>
</tr>
<tr>
<td>Myoclonus – Muscle twitching (spontaneous or inducible)</td>
<td>Hyperthermia: Mild&lt;8.5°C, severe ≥38.5°C</td>
<td>Agitation - restlessness</td>
</tr>
<tr>
<td>Ocular Clonus</td>
<td>Hypertension</td>
<td>Memory loss</td>
</tr>
<tr>
<td>Weakness</td>
<td>Diaphoresis</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Trembling, shivering or shaking</td>
<td>Mydriasis</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Akathisia – restlessness</td>
<td>Diarrhoea</td>
<td>Hypomania</td>
</tr>
<tr>
<td>Hypertonia – rigidity</td>
<td>Fever</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Bradykinesia – slow movements</td>
<td>Seizures Weakness</td>
<td>Coma</td>
</tr>
</tbody>
</table>

Refs: 20, 64, 68, 74
Serotonin Syndrome

The sequence of symptoms, most common first:

- Headache
- Feeling sick
- Diarrhoea
- High temperature, shivering, sweating
- High blood pressure, fast heart rate
- Tremor, muscle twitching, over-responsive reflexes
- Convulsions (fits)
- Agitation, confusion, hallucinations
- Loss of consciousness (coma) \(^{20}\)
Serotonin Syndrome

Patients who have genetic intolerance to serotonin-active drugs\textsuperscript{71} \/ antidepressants\textsuperscript{75} are more likely to be susceptible to serotonin syndrome.

Serotonin Syndrome can occur within 1 to 6 days of a change in serotonin medication.\textsuperscript{76} Over 85\% of doctors are unaware of serotonin syndrome as a clinical diagnosis” \textsuperscript{64,77} which is serious as this condition needs to be recognised in order to reduce morbidity and fatalities.\textsuperscript{78}
Target Organ Toxicity

Target Organ Toxicity is eventual cell death within body organs due to chronic exposure to medication.

Long-term psychiatric medication exposure creates toxic changes within the tissues of the brain, which amount to chemical brain injury, and neurological brain damage with physical and psychological deterioration.\(^7\)

Epidemiology studies indicate exposure to antidepressant medication results in developing risks of dementia, strokes and Parkinson’s Disease,\(^79\text{–}81\) which are relatively unknown long-term antidepressant ADR.
Movement Disorders

“…SRIs are clearly capable of causing parkinsonian side effects, akathisia, and dyskinetic movements that may resemble tardive dyskinesia.”\textsuperscript{82} and “the majority of SSRI-related reactions appear to occur within the first month of treatment.”\textsuperscript{83}

Even though the incidence for some EPS adverse reactions is low, “Clinicians should be cognizant of the potential for these reactions, as prompt recognition and management is essential in preventing potentially significant patient morbidity.”\textsuperscript{84}
Movement Disorders

In a comprehensive review of SSRI-induced Extra Pyramidal Symptoms (EPS)\textsuperscript{85} the following side effects were found:

- Akathisia (45%)
- Dystonia (28%)
- Parkinsonism (14%)
- Tardive dyskinesia-like states (11%)

These movement disorders are probably associated with serotonin disruption\textsuperscript{86} and interactions with dopamine and norepinephrine neurotransmitters.\textsuperscript{87}
**Akathisia**

Akathisia may be due to SSRI serotonergic activity disrupting dopamine equilibrium.\(^{86,87}\) and has been described as the most common neurological symptom.\(^{88}\)

The symptoms of akathisia manifest as extreme involuntary motor restlessness, accompanied by mental changes such as agitation and inner restlessness.\(^{89,90}\)

Restlessness and agitation, a classic description of akathesia, is a mental health change associated with serotonin syndrome. Since serotonin syndrome is more likely to occur in patients with a genetic intolerance, akathisia, due to a “possibly deficient cytochrome P450 (CYP) isoenzyme status”\(^{86}\) is more than likely.
Akathisia

The NICE guideline for Depression describes akathisia in association with the commencement of SSRIs, as “anxiety”. Due to akathisia predisposing suicide ideation, suicide and violence, “anxiety” is an underestimation of the potential serious nature of akathisia, and a misinterpretation of it’s origin.

Akathisia was added as a side effect of the SSRI Seroxat in 2003, following the BBC Panorama broadcasts of 2002.

Akathesia is associated with CYP450 2D6, 2C19 and 2C9 variant genotypes and the short allele of the serotonin transporter gene-linked polymorphic region (5HTTLPR).
Dystonia

Acute dystonia is known to be associated with SSRI antidepressants. \textsuperscript{104}

Dystonia is characterised by involuntary neck and trunk twisting movements, or abnormal postures. \textsuperscript{104, 105}

These are painful, sustained and disfiguring muscle spasms, due to dysfunction or over-activity, in the brain structures that control movement.
Parkinsonism/Extra Pyramidal Symptoms (EPS)

“EPS have been reported with different classes of antidepressants, are not dose related, and can develop with short-term or long-term use. In view of the risk for significant morbidity and decreased quality of life, clinicians must be aware of the potential for any class of antidepressants to cause these adverse effects.” CYP450 2D6 diminished drug elimination variant genotype is a risk factor for EPS in the elderly and others.

The symptoms of parkinsonism or Extra Pyramidal Symptoms (EPS) include:

- Body tremor, flat, vacant expression, zombie appearance, excessive salivation (unable to swallow)
- Bradykinesia, the slowing down and rigidity of large muscle movement so that the patient appears clumsy.
- Shuffling gait
Parkinson’s Disease and Curtailed Life Span

A five year retrospective case controlled study in Denmark\textsuperscript{81} showed the “risk of developing Parkinsons disease was approximately doubled by exposure to antidepressants.”\textsuperscript{7}

15% of patients (aged 30 and older) who were prescribed antidepressants died within five years.\textsuperscript{81}
Tardive Dyskinesia

Tardive Dyskinesia, which is more often seen in men,\textsuperscript{111} is probably due to known SSRI motor neuron toxicity with loss of specific brain cells\textsuperscript{112} and is related to Target Organ Toxicity.\textsuperscript{7}

Tardive dyskinesia is characterized by repetitive involuntary movements ranging from restless legs to abnormal body movements and facial grimacing. Rapid purposeless movements of the arms, legs, and trunk may also occur and involuntary movements of the fingers may be present.\textsuperscript{113}

Those with CYP2D6 diminished variant genotype have a greater risk of developing tardive dyskinesia.\textsuperscript{114}

Orofacial dyskinesias\textsuperscript{115} are disfiguring and include teeth grinding,\textsuperscript{116, 117} eye tics,\textsuperscript{118} grimacing, tongue protrusion, lip smacking, puckering and pursing of the lips.
Dementia

With long-term antidepressant use, 4-6% patients developed dementia within ten years and the relative risk of new onset dementia was 2 to 5 fold compared to the non-drug exposed.\textsuperscript{79}

Animal studies show exposure to SSRIs results in cell death and shrinkage in the hippocampus.\textsuperscript{119,120} Neuroimaging studies of human brains show 10-19% smaller hippocampi in SSRI medicated and formerly medicated patients compared to matched controls.\textsuperscript{121,122}

The hippocampus is the area of the brain involved in connecting, organising and forming memories, spatial awareness, navigation and emotional responses and in Alzheimers disease deterioration causes memory problems and disorientation.
**Haemorrhage**

Increased risk for upper gastrointestinal bleeds.\(^{123, 124, 125}\)

**Mechanism:**
- Serotonin is released by blood platelets, which are dependent on a serotonin transporter for the uptake of serotonin.
- SSRIs block the serotonin transporter preventing the uptake of serotonin into platelets, which causes problems with blood clotting, leading to haemorrhage.

**Gastrointestinal bleeding** was added as a side effect on UK Patient Information Leaflets for SSRI Seroxat in June 2003, after the BBC Panorama broadcasts.\(^{100, 101}\) SSRIs in general increase the risk of upper GI bleeding.\(^{124}\)
Strokes

In an antidepressant case-controlled study over five years, the risk of strokes increased by 20-40%, new strokes occurred in 13.4% of patients and 70% of strokes occurred among patients before the age of 65.\textsuperscript{80}

Use of SSRI antidepressants with higher affinity for the serotonin transporter was associated with a statistically significant increase in risk for stroke. 776 strokes occurred in 21,462 patients taking SSRI antidepressants and 434 strokes in 14,927 patients taking antidepressants with lesser affinity for the serotonin transporter.\textsuperscript{126}

Seizures or Convulsions

SSRIs reduce seizure threshold and provoke epileptic seizures.\textsuperscript{127,128}

CYP2D6 and CYP2C19 genetic variants (or polymorphisms) are potential risk factors for seizures and muscle jerks and spasms (myoclonus).\textsuperscript{129}
Ocular Adverse Reactions

Glaucoma and intraocular pressure alterations with SSRIs: Serotonin plays a role in the control of intraocular pressure (IOP) and there is evidence for IOP modifications in patients receiving SSRIs.\(^ {130, 131} \)

“In all cases reported in the literature the angle-closure glaucoma represents the most important SSRI-related ocular adverse event.”\(^ {132} \)

Visual disturbances such as ocular clonus\(^ {64} \) (involuntary eye movements) blurred vision and difficulty focusing impact adversely upon driving ability.\(^ {20} \)
Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), more often associated with antipsychotic drugs, is a rare SSRI adverse reaction that is dangerous when the symptoms are attributed to an infection, not detected and treated\textsuperscript{20} and potentially fatal.\textsuperscript{133}

Mortality/ Morbidity
The incidence of mortality from NMS is estimated at 5-11.6%.\textsuperscript{134} Death usually results from respiratory failure, cardiovascular collapse, myoglobinuric renal failure, arrhythmias, or diffuse intravascular coagulation. Morbidity from NMS includes rhabdomyolysis, pneumonia, renal failure, seizures, arrhythmias, diffuse intravascular coagulation, and respiratory failure.\textsuperscript{134}
Neuroleptic Malignant Syndrome

Encephalitis, a viral brain inflammation, has similar symptoms to NMS.

<table>
<thead>
<tr>
<th>High temperature</th>
<th>Sweating</th>
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<td>Unstable blood pressure: high &amp; low</td>
<td>Pale skin</td>
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<tr>
<td>Irregular heart beat: Arrhythmia</td>
<td>Tremor</td>
</tr>
<tr>
<td>Rapid heartbeat: Tachycardia</td>
<td>Muscle Rigidity/stiffness</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Kidney failure</td>
</tr>
<tr>
<td>Elevated creatinine phosphokinase (CPK) - a sign of muscle breakdown</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Increased White Blood Cell Count</td>
<td>Difficulty in speaking</td>
</tr>
<tr>
<td>Agitation</td>
<td>Seizures</td>
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</tbody>
</table>

Refs 20, 134, 135
Polypharmacy

Polypharmacy is the combined use of drugs.

Psychotropic polypharmacy, which includes SSRIs, is associated with:
- Increased risk of Sudden Cardiac Death at the time of an acute coronary event.\textsuperscript{136}
- Serotonin Syndrome.\textsuperscript{67}
- NMS.\textsuperscript{135}

Polypharmacy with SSRI and general medications is associated with:
- Increased risk of death from breast cancer with Tamoxifen and Paxil.\textsuperscript{137}
- Increased risk of stokes with SSRI and nonsteroidal anti-inflammatory drugs or low-dose aspirin.\textsuperscript{124}
- Serotonin Syndrome when additional drugs inhibit CYP2D6,\textsuperscript{138, 139} CYP3A4, CYP1A2, CYP2C9/10 and CYP2C19.\textsuperscript{139}
- Seizures when additional drugs inhibit CYP2D6.\textsuperscript{129}

Polypharmacy compounds ADRs in Poor Metabolisers of psychotropic drugs.
Pregnancy

"Antidepressant use during pregnancy is associated with increased risks of miscarriage, birth defects, preterm birth, newborn behavioural syndrome, persistent pulmonary hypertension of the newborn and possible longer term neurobehavioral effects.” 140

Miscarriage
- SSRIs use during the first trimester has a 61% increased risk of miscarriage.141,142

Preterm Birth
- Antidepressant use points to increased risk for early delivery in women which incurs many short- and long-term health problems risks to babies born before 37 weeks.140,143
Fetal effects

Maternal antidepressant use and adverse fetal effects\textsuperscript{144} include:

- Increased motor activity in the first trimester and at the end of the second trimester.
- The disruption of quiet sleep in the third trimester with continual body movement.
- Poor inhibitory motor control during sleep state near full term.
Neonatal Effects

Maternal SSRI use is associated with the following neonatal effects:

**Birth Defects**
- **Anencephaly**: Absence of a large part of the brain and the skull.\(^{145}\)
- **Craniosynostosis**: Premature ossification of skull sutures.\(^{145}\)
- **Omphalocele**: Intestines, liver, and other organs lie in a sac external to abdomen.\(^{145}\)
- **Spina bifida\(^{20}\)**
- **Cleft palate and hare lip\(^{20}\)**

**Cardiac Defects**
- **Heart rate variability\(^{146}\)** with prolonged QT intervals,\(^ {147}\) which is a risk factor for sudden death.\(^ {148}\)
- **Ventricular and atrial malformations in the newborn.\(^ {92}\)**
Neonatal Effects

Haemorrhage (SSRIs disrupt platelet formation)
- Intraventricular (brain) haemorrhage.\textsuperscript{149}
- Subarachnoid haemorrhages.\textsuperscript{150}

Convulsions
- Third-trimester SSRI use is associated with infant convulsions.\textsuperscript{151}

Persistent Pulmonary Hypertension
- Life threatening neonatal condition requiring respiratory support and drug treatment to induce vasodilation of the pulmonary vessels.\textsuperscript{152}

Other Effects for third-trimester SSRI use:
- Problem feeding, lethargy, respiratory distress and gastrointestinal symptoms.\textsuperscript{153}
- Reduced neonatal weight gain and growth curve.\textsuperscript{154}
Neonatal Neurobehavioral Effects

Neurobehavioral Effects

- Rapid-eye-movement sleep and more spontaneous startles and sudden arousals.\textsuperscript{146}

Long-term Neurobehavioral Effects

- Two-fold increased risk of autism-spectrum disorders when mothers use SSRIs one year prior to delivery\textsuperscript{155} with the strongest effect associated during the first trimester.\textsuperscript{143}
SSRI neonatal withdrawal effects in infants are associated with mothers who used an antidepressant during the third trimester.  

- Agitation, poor feeding, hypotonia, lethargy, gastrointestinal symptoms, convulsions, tremor, fever and respiratory distress, weak cry and extensor posturing with back-arching.

- Low blood sugar and fits.

- Restlessness and irritability.

- Breathing difficulties, seizures and constant crying.

- Poor feeding muscle rigidity and jitteriness.
Neonatal Serotonergic Toxicity Syndrome

Serotonergic toxicity syndrome symptoms include, jitteriness, tachypnoea, temperature instability, tremors and increased muscle tone,\textsuperscript{159} replicating withdrawal effects.

“Differentiating between these two syndromes in the neonate presents a dilemma for clinicians,”\textsuperscript{160} but can be diagnosed by placental cord blood tests as the severity of serontonergic effects is “significantly related to placental cord blood 5-HIAA levels”\textsuperscript{161} which confirms SSRI transfer through the placenta.\textsuperscript{162}
Withdrawal/Discontinuation

SSRI discontinuation may cause ADR withdrawal events\textsuperscript{156, 163–166} being more common with the SSRIs having a short half-life.\textsuperscript{167, 168}

Prozac brain levels are 100 times greater than blood levels, indicating evidence of toxic brain levels and believed to be replicated by other SSRIs. The accumulation of drug residue, evidenced by patients’ reports, produces a delayed withdrawal perpetuating drug reactions that continue during Prozac use and for a long time after discontinuation.\textsuperscript{169}

Many personal accounts relate of the difficulties of withdrawal from antidepressants,\textsuperscript{170, 171} causing problems resulting in patients remaining on long term medication, if GP support is unavailable.\textsuperscript{172}
Withdrawal/Discontinuation

Discontinuation symptoms are different from a relapse or recurrence,\textsuperscript{173} therefore health care professionals need to be educated about the potential adverse effects of SSRI discontinuation.\textsuperscript{174,175}

The habit forming potential of Seroxat was acknowledged in June 2003, 8 months after the BBC Panorama programme “Secrets of Seroxat”\textsuperscript{101} when wording was removed from the Patient Information Leaflet that previously denied the habit forming potential of Seroxat.
## Physical Withdrawal Reactions

<table>
<thead>
<tr>
<th>SSRIs:</th>
<th>Physical symptoms</th>
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<tbody>
<tr>
<td></td>
<td>Nausea and Vomiting</td>
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<tr>
<td></td>
<td>Abdominal pain</td>
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<tr>
<td></td>
<td>Diarrhoea, Flatulence</td>
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<td>General discomfort</td>
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<td>Sweating</td>
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<td>Headaches</td>
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<td>Extreme Restlessness</td>
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<td>Fatigue</td>
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<td></td>
<td>Chills</td>
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<td></td>
<td>Flu like symptoms</td>
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</tbody>
</table>

**Refs:** 171, 176 – 179
Physical ADRs linked to Antidepressant/Gene Variant Interactions

Hyponatraemia:
CYP450 2D6 diminished drug elimination variant genotype.\textsuperscript{12}

Cardiovascular Toxicity:
CYP450 2D6 diminished drug elimination variant genotype.\textsuperscript{62}

Serotonin Syndrome Toxicity:
CYP450 2D6 diminished drug elimination variant genotypes.\textsuperscript{72, 73, 138, 139}

Extra Pyramidal Symptoms (EPS):
CYP450 2D6 diminished drug elimination variant genotype.\textsuperscript{107, 108, 113}

Tardive Dyskinesia
CYP2D6 diminished drug elimination variant genotype.\textsuperscript{114}

Akathesia:
CYP450 2D6, 2C19 and 2C9 drug elimination variant genotypes.\textsuperscript{102} Short allele of the serotonin transporter gene-linked polymorphic region (5HTTLPR).\textsuperscript{103}

Research associating genotype variants far all antidepressant physical ADRs is limited and needs further exploration.
Conclusion

Currently professionals and patients are insufficiently informed about SSRI adverse drug reactions, which have a major public health impact.

An informed consent can be based upon intelligent choices facilitated by the provision of extensive information about SSRI adverse reactions in this document.

The introduction of pharmacogenetic testing prior to antidepressant prescribing,\textsuperscript{64} would show professional responsibility and accountability for the patient’s physical and emotional safety, and welfare.
References:


(3) NHS The Information Centre for Health and Social Care “Copyright © 2012, Reused with the permission of the Health and Social Care Information Centre. www.ic.nhs.uk


(7) Jackson, Grace E. MD. (2009), "Drug-Induced DEMENTIA a Perfect Crime" Bloomington, IN: Author House.


http://pmj.bmj.com/content/81/957/429.full

(16) NHS Choices Diabetes, type 2 - Symptoms
http://www.nhs.uk/Conditions/Diabetes-type2/Pages/Symptoms.aspx


(20) MIND Making Sense of Antidepressants: written for Mind by Katherine Darton  


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2918297/


(28) Hyponatraemia from Wikipedia  
http://en.wikipedia.org/wiki/Hyponatremia


Source: Khawam EA., Laurencic G., Malone DA., MD. “Side effects of antidepressants: An overview” Cleveland Clinic Journal of Medicine, Vol 73, No. 4, April 2006, p.351-361

Source: Khawam EA., Laurencic G., Malone DA., MD. “Side effects of antidepressants: An overview” Cleveland Clinic Journal of Medicine, Vol 73, No. 4, April 2006, p.351-361


(49) Charles V. Clevenger et al, The Role of Prolactin in Mammary Carcinoma Endocrine Reviews February 1, 2003 vol. 24 no. 1 1-27 http://edrv.endojournals.org/content/24/1/1.full
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2024771/?tool=pmcentrez


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC471069/

(54) Baker S. SSRIs May Cause Sudden Cardiac Death In Women
http://rense.com/general85/anti.htm


(59) Xiong GL. et al. Prognosis of Patients Taking Selective Serotonin Reuptake Inhibitors Before Coronary Artery Bypass Grafting American Journal of Cardiology Volume 98, Issue 1, Pages 42-47, 1 July 2006 http://www.ajconline.org/article/S0002-9149%2806%2900565-0/abstract


(65) FDA Alert 2006 Serotonin Syndrome
Public Health Advisory: Combined Use of 5-Hydroxytryptamine Receptor Agonists (Triptans), Selective Serotonin Reuptake Inhibitors (SSRIs) or Selective Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs) May Result in Life-threatening Serotonin Syndrome. Rockville, MD: Center for Drug Evaluation and Research; July 19, 2006.

(66) Gillman, P.K. Serotonin toxicity, serotonin syndrome: Created on Tuesday, 22 May 2012 Last Updated on Thursday, 14 June 2012 03:01
PsychoTropical Research ©Dr Ken Gillman MRC Psych


(68) Serotonin Syndrome Choice and Medication. Information for people who use services, carers and professionals.

(69) Patient UK Serotonin Syndrome
www.patient.co.uk/doctor/Serotonin-Syndrome.htm


http://www.medsafe.govt.nz/profs/PUArticles/SerotoninSyndromeToxicityReminder.htm

(75) Kircheiner J. et al. “Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response.” Molecular Psychiatry March 2004,9, p442-473. 
http://www.nature.com/mp/journal/v9/n5/full/4001494a.html

(76) Information for Healthcare Professionals: Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), 5-Hydroxytryptamine Receptor Agonists (Triptans) FDA ALERT [7/2006] 


Source: Jackson, Grace E. MD. (2009), "Drug-Induced Dementia a Perfect Crime" Bloomington, IN: Author House. p.60


(91) The NICE guideline on the Treatment and Management of depression in Adults October 2010 Section 11.10.2 Suicidality and Antidepressants. p.464

http://www.springer.com/cda/content/document/cda_downloaddocument/9781603274340-c1.pdf?SGWID%3


(95) S. Donovan, M. Kelleher, J. Lambourn and T. Foster, The occurrence of suicide following the prescription of antidepressant drugs, Archives of Suicide Research 5 (1999), 181–192. http://www.springerlink.com/content/9fxjj13wqj91eepm/


(99) Pringle E. “SSRI-Induced Akathisia's Link To Suicide and Violence” Lawyers and Settlements.com August 18, 2007, 09:00:00AM.  

http://books.google.co.uk/books?id=UDklewA6SIEC&pg=PA117&lpg=PA117&dq

(101) BBC News Panorama “The Secrets of Seroxat” October 2002  
http://news.bbc.co.uk/1/hi/programmes/panorama/2310197.stm


(110) Bradykinesia - Drug induced: SSRIs
http://endoflifecare.tripod.com/juvenilehuntingtons Disease/id60.html


(117) Bostwick JM. MD. and Jaffee MS. MD. Buspirone as an antidote to SSRI-Induced Bruxism in 4 Cases. J Clin Psychiatry 60:12, December 1999 https://dentsem.com/assets/docs/Dr_Spensor_Maui_Buspirone_as_an_Antidote_to_SSRI-Induced_Bruxism_in_4_Cases.pdf

Source: Jackson, Grace E. MD. (2009), "Drug-Induced Dementia a Perfect Crime" Bloomington, IN: Author House. p. 111

Source: Jackson, Grace E. MD. (2009), "Drug-Induced Dementia a Perfect Crime" Bloomington, IN: Author House. p. 121
Source: Jackson, Grace E. MD. (2009), "Drug-Induced Dementia a Perfect Crime" Bloomington, IN: Author House. p. 129

Source: Jackson, Grace E. MD. (2009), "Drug-Induced Dementia a Perfect Crime" Bloomington, IN: Author House. p. 130

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2825017/?tool=pmcentrez


(133) British National Formulary, (BNF) September 2006, Section 4.3.1: Tricyclics and related antidepressant drugs, Antimuscarinic drugs. Side-effects. p. 200. bnf.org


(141) Antidepressants Linked to Miscarriage Risk
Researchers See Possible Connection Between SSRI and Miscarriages
By Katrina Woznicki, WebMD Health News, Reviewed by Laura J. Martin, MD
http://miscarriage.about.com/b/2010/06/02/study-finds-ssri-antidepressants-link-to-increased-miscarriage-risk.htm

(143) Harvard Medical School News: HMS researchers at Beth Israel Deaconess Medical Center - Study Links Pregnancy Risks, Antidepressants SSRIs and pregnancy. October 31, 2012
http://hms.harvard.edu/content/study-links-pregnancy-risks-antidepressants


(152) Koren G., SSRIs and persistent pulmonary hypertension of the newborn BMJ 2012;344:d7642 http://www.bmj.com/content/344/bmj.d7642


(158) Canada Health advisory. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns. August 9, 2004

(159) Isbister GK. et al. Neonatal paroxetine withdrawal syndrome or actually serotonin syndrome? Letters to the editor. Arch Dis Child Fetal Neonatal Ed 2001;85:F145 (September)
http://www.antidepressantsfacts.com/paxil-serotonin-toxicity.htm


(170) Social Audit: Reports of Withdrawal Reactions http://www.socialaudit.org.uk/425ssritable.htm#REPORTS
(171) MIND “Making sense of coming off psychiatric drugs”
http://www.mind.org.uk/help/medical_and_alternative_care/making_sense_of_coming_off_psychiatric_drugs#antidepressants

http://www.bmj.com/content/339/bmj.b3999


Contributors:

Catherine Clarke SRN, SCM, MSSCH, MBChA
Jan Evans MCSP. Grad Dip Phys

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