Antidepressant
SSRI
Physical
Adverse Drug Reactions

Contents

Contents

Contents

Contents

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.[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[5] such as dopamine, histamine, adrenaline, noradrenaline and acetylcholine.[6]

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 feed back 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.**[8] 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.[9] Other drug metabolising enzymes such as CYP450 pathways play an important role in SSRI responses.[10]

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 pharmacogentic 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." [5] 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.[5]

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.[5] 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[5] and withdrawal symptoms can last for weeks or months.[13]

See: Physical Withdrawal Reactions. Page 61.

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[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.[5]

Physical effects of raised cortisol are weight gain, immune dysfunction and atrophy of the hippocampus with memory loss.[5]

Long term raised cortisol causes insulin resistance,[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[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.[25, 26, 27] 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.

Hyperprolactinaemia, an excess of prolactin, is caused by SSRI's disruption to the endocrine system. [29, 30, 31] In a French pharmacovigilance database study, 17% of drug induced hyperprolactinaemia cases had been induced by SSRIs.[32]

Hyperprolactinaemia 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.[33, 34] Sexual dysfunction effects continue as long as the drug is taken [6] and may persist after the drug is withdrawn and continue indefinitely.[20]

Symptoms include:

Male	Female
Decreased libido	Decreased libido
Erectile dysfunction	Lactation - Galactorrhoea
Gynecomastia: breast enlargement	Menstrual irregularity
Hypogonadism: testicular atrophy	Amenorrhoea: absent menstruation
Priapism – persistent erection	Anovulation
Infertility	Delayed orgasm & anorgasmia
Milk secretion – Galactorrhoea	Infertility

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.[32, 37, 38]

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

SSRIs are linked with greater susceptibility to bone fractures[41] and the risk may be increased with higher doses.[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[43] and SSRI use in adults aged 50 and older is associated with a 2-fold increased risk of clinical fragility fracture.[44]

Prolonged SSRI use causes a significant risk of non- vertebral fractures[45] such as hip fractures in the elderly.[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. [47, 48]

"Prolactin hormone functions to stimulate the growth and motility of human breast cancer cells." [49] and is confirmed by research in rats which depicts carcinogenesis of the male mammary gland following an induced secretion of pituitary prolactin.[50]

When SSRIs are taken for 36months or longer there is an increased risk of breast cancer although the association of hyperprolactinaemia and SSRIs is not yet clear. [32]

Cardiac Disease

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

SSRIs can cause death due to cardiac arrest,[53] and may cause sudden cardiac death in women.[54] Abnormal changes in the electrical activity of the heart[55] such as ventricular arrhythmias[56, 57] are associated with an increased risk of myocardial infarction.[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 [64, 65, 66] due to excessive serotonin levels in the brainstem and spinal cord, incurred by SSRIs causing serotonin toxicity.[67, 68, 69]

Precipitating factors for Serotonin Syndrome:

- The consecutive use of SSRIs.[70, 71]
- Raising SSRI dose.[64]
- Prescribing of two serotonergic drugs simultaneously.[67, 65]
- SSRI with either MAOIs, tryptophan or lithium.[20]
- Abrupt withdrawal of antidepressants.[64]
- CYP450 diminished drug elimination variant genotype,[72] Intermediate CYP 2D6[73] and Poor CYP 450 Metabolisers.

Serotonin Syndrome

There is a triad of clinical symptoms[64, 74] which range from being barely perceptible to fatal.[64]

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

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[71] /antidepressants[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.[76] Over 85% of doctors are unaware of serotonin syndrome as a clinical diagnosis" [64, 77] which is serious as this condition needs to be recognised in order to reduce morbidity and fatalities.[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 – 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."[82] and "the majority of SSRI-related reactions appear to occur within the first month of treatment." [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." [84]

Movement Disorders

In a comprehensive review of SSRI-induced Extra Pyramidal Symptoms (EPS)[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[86] and interactions with dopamine and norepinephrine neurotransmitters.[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”.[91]
Due to akathisia predisposing suicide ideation,[92, 93] suicide[94 – 97] and violence,[98, 99] “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. [100, 101]

Akathesia is associated with CYP450 2D6, 2C19 and 2C9 variant genotypes[102] and the short allele of the serotonin transporter gene-linked polymorphic region (5HTTLPR).[103]

Dystonia

Acute dystonia is known to be associated with SSRI antidepressants.[104]

Dystonia is characterised by involuntary neck and trunk twisting movements, or abnormal postures.[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."[106] CYP450 2D6 diminished drug elimination variant genotype is a risk factor for EPS in the elderly[107] and others.[108, 109]

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

- Body tremor, flat, vacant expression, zombie appearance, excessive salivation (unable to swallow)
- Bradykinesia,[110] 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**[81] showed the "risk of developing **Parkinsons disease** was approximately doubled by exposure to antidepressants." [7]

15% of patients (aged 30 and older) who were prescribed antidepressants died within five years.[81]

Tardive Dyskinesia

Tardive Dyskinesia, which is more often seen in men,[111] is probably due to known SSRI motor neuron toxicity with loss of specific brain cells[112] and is related to Target Organ Toxicity.[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.[113]

Those with CYP2D6 diminished variant genotype have a greater risk of developing tardive dyskinesia.[114]

Orofacial dyskinesias[115] are disfiguring and include teeth grinding,[116, 117] eye tics,[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.[79]

Animal studies show exposure to SSRIs results in cell death and shrinkage in the hippocampus.[119, 120] Neuroimaging studies of human brains show 10-19% smaller hippocampi in SSRI medicated and formerly medicated patients compared to matched controls.[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.[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.[126]

Seizures or Convulsions

SSRIs reduce seizure threshold and provoke epileptic seizures.[127, 128]

CYP2D6 and CYP2C19 genetic variants (or polymorphisms) are potential risk factors for seizures and muscle jerks and spasms (myoclonus).[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 focussing 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[20] and potentially fatal.[133]

Mortality/ Morbidity

The incidence of mortality from NMS is estimated at 5-11.6%.[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.[134]

Neuroleptic Malignant Syndrome

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

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

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.[136]
- Serotonin Syndrome.[67]
- NMS.[135]

Polypharmacy with SSRI and general medications is associated with:

- Increased risk of death from breast cancer with Tamoxifen and Paxil.[137]
- Increased risk of stokes with SSRI and nonsteroidal anti-inflammatory drugs or low-dose aspirin.[124]
- Serotonin Syndrome when additional drugs inhibit **CYP2D6,**[138, 139] **CYP3A4, CYP1A2, CYP2C9/10** and **CYP2C19.**[139]
- Seizures when additional drugs inhibit CYP2D6.[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[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.[149]
- Subarachnoid haemorrhages.[150]

Convulsions

- Third-trimester SSRI use is associated with infant convulsions.[151]

Persistent Pulmonary Hypertension

- Life threatening neonatal condition requiring respiratory support and drug treatment to induce vasodilation of the pulmonary vessels.[152]

Other Effects for third-trimester SSRI use:

- Problem feeding, lethargy, respiratory distress and gastrointestinal symptoms.[153]
- Reduced neonatal weight gain and growth curve.[154]

Neonatal Neurobehavioral Effects

Neurobehavioral Effects

- Rapid-eye-movement sleep and more spontaneous startles and sudden arousals.[146]

Long-term Neurobehavioral Effects

- Two-fold increased risk of autism-spectrum disorders when mothers use SSRIs one year prior to delivery[155] with the strongest effect associated during the first trimester.[143]

Neonatal Withdrawal Effects Syndrome

SSRI neonatal withdrawal effects in infants are associated with mothers who used an antidepressant during the third trimester.[156]

- Agitation, poor feeding, hypotonia, lethargy, gastrointestinal symptoms, convulsions, tremor, fever and respiratory distress, weak cry and extensor posturing with, back-arching.[147]
- Low blood sugar and fits.[20]
- Restlessness and irritability.[157]
- Breathing difficulties, seizures and constant crying.[158]
- Poor feeding muscle rigidity and jitteriness.[157, 158]

Neonatal Serotonergic Toxicity Syndrome

Serotonergic toxicity syndrome symptoms include, jitteriness, tachypnoea, temperature instability, tremors and increased muscle tone,[159] replicating withdrawal effects.

"Differentiating between these two syndromes in the neonate presents a dilemma for clinicians,"[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"[161] which confirms SSRI transfer through the placenta.[162]

Withdrawal/Discontinuation

SSRI discontinuation may cause ADR withdrawal events[156, 163 – 166] being more common with the SSRIs having a short half-life.[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.[169]

Many personal accounts relate of the difficulties of withdrawal from antidepressants,[170, 171] causing problems resulting in patients remaining on long term medication, if GP support is unavailable.[172]

Withdrawal/Discontinuation

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

The habit forming potential of Seroxat was acknowledged in June 2003, 8 months after the BBC Panorama programme "Secrets of Seroxat"[101] when wording was removed from the Patient Information Leaflet that previously denied the habit forming potential of Seroxat.

Physical Withdrawal Reactions

SSRIs:

- citalopram
- escitalopram
- prozac/fluoxetine
- seroxat/paroxetine
- sertraline/lustral
- fluvoxamine/faverin

Physical symptoms	
Nausea and Vomiting	Numbness
Abdominal pain	Pins and needles, tingling
Diarrhoea, Flatulence	Electric shock sensations
General discomfort	Disturbed Temperature
Sweating	Tremor, Muscle spasms
Headaches	Dizziness
Extreme Restlessness	Light Headedness
Fatigue	Vertigo, loss of balance
Chills	Insomnia
Flu like symptoms	Suicidal thoughts/actions

Refs: 171, 176 – 179

Physical ADRs linked to Antidepressant/Gene Variant Interactions

Hyponatraemia:
CYP450 2D6 diminished drug elimination variant genotype.[12]

Cardiovascular Toxicity:
CYP450 2D6 diminished drug elimination variant genotype.[62]

Serotonin Syndrome Toxicity:
CYP450 2D6 diminished drug elimination variant genotypes.[72, 73, 138, 139]

Extra Pyramidal Symptoms (EPS):
CYP450 2D6 diminished drug elimination variant genotype. [107, 108, 113]

Tardive Dyskinesia
CYP2D6 diminished drug elimination variant genotype.[114]

Akathesia:
CYP450 2D6, 2C19 and 2C9 drug elimination variant genotypes.[102] Short allele of the serotonin transporter gene-linked polymorphic region (5HTTLPR).[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,[64] would show professional responsibility and accountability for the patient's physical and emotional safety, and welfare.

References:

(1) The NICE guideline on the Treatment and Management of depression in Adults October 2010 p.305 http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf

(2) Common mental health disorders. Identification and pathways to care Issue date: May 2011 http://www.nice.org.uk/nicemedia/live/13476/54520/54520.pdf

(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

(4) Philip W. Long MD., Drug Monograms: Fluoxetine and Citalopram Internet Mental Health 1995-1999.

(5) Jackson, Grace E. MD. (2005), *"Rethinking Psychiatric Drugs: A Guide for Informed Consent"* Bloomington, IN: Author House.

(6) 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 http://ccjm.org/content/73/4/351.full.pdf

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

(8) Van Bortel L. Symposium "Clinical Pharmacology Anno 2008". 10th Heymans Memorial Lecture. Verh K Acad Geneeskd Belg. 2009;71(6):315-34. http://www.ncbi.nlm.nih.gov/pubmed/20232787

(9) Malhotra AK, Murphy GM Jr, Kennedy JL., Pharmacogenetics of psychotropic drug response. Am J Psychiatry. 2004 May;161(5):780-96. Review http://www.ncbi.nlm.nih.gov/pubmed/15121641

(10) Serretti A, Artioli P. The pharmacogenomics of selective serotonin reuptake inhibitors. Pharmacogenomics J. 2004;4(4):233-44. Review. http://www.ncbi.nlm.nih.gov/pubmed/15111987

(11) Crisafulli C, Fabbri C, Porcelli S, Drago A, Spina E, De Ronchi D, Serretti A. Pharmacogenetics of antidepressants. Front Pharmacol. 2011;2:6. Epub 2011 Feb 16. http://www.ncbi.nlm.nih.gov/pubmed/21687501

(12) Kwadijk-de Gijsel, S., et al "Variation in the CYP2D6 gene is associated with a lower serum sodium concentration in patients on antidepressants" Br J Clin Pharmacol. 2009 August; 68(2): 221–225. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2767286/pdf/bcp0068-0221.pdf

(13) Haddad Peter M. and Anderson Ian M. Recognising and managing antidepressant discontinuation symptoms. Advances in Psychiatric Treatment (2007) 13: 447-457 http://apt.rcpsych.org/content/13/6/447.full

(14) Seifritz E, et al, Neuroendocrine effects of a 20-mg citalopram infusion in healthy males. A placebo-controlled evaluation of citalopram as 5-HT function probe. Neuropsychopharmacology. 1996 Apr;14(4):253-63. http://www.ncbi.nlm.nih.gov/pubmed/8924193

Source: Jackson Grace E. MD (2005) *"Rethinking Psychiatric Drugs: A Guide for Informed Consent"*. Bloomington, IN: Author House. p.90

(15) Vale S., Psychosocial stress and cardiovascular diseases, Postgrad Med J 2005;81:429-435 doi:10.1136/pgmj.2004.028977
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

(17) Andersohn F, Schade R, Suissa S, Garbe E. Long-term use of antidepressants for depressive disorders and the risk of diabetes mellitus. Am J Psychiatry. 2009 May;166(5):591-8. Epub 2009 Apr 1. http://www.ncbi.nlm.nih.gov/pubmed/19339356

(18) Kivimäki M., PHD, et al., "Antidepressant Medication Use, Weight Gain, and Risk of Type 2 Diabetes. A population-based study." Diabetes Care. 2010 December; 33(12): 2611–2616.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2992199/

(19) Mercola J., “Dangerous Antidepressants Elevate Diabetes Risk” June 29 2006 http://articles.mercola.com/sites/articles/archive/2006/06/29/dangerous-antidepressants-elevate-type-2-diabetes-risk.aspx

(20) MIND Making Sense of Antidepressants: written for Mind by Katherine Darton http://www.mind.org.uk/help/medical_and_alternative_care/making_sense_of_antidepressants#sideeffects

(21) Levkovitz Y., “Antidepressants induce cellular insulin resistance by activation of IRS-1 kinases” Original Research Article: Molecular and Cellular Neuroscience, Volume 36, Issue 3, November 2007, Pages 305-312 http://www.sciencedirect.com/science/article/pii/S1044743107001339

(22) Kirpekar, Vivek C. and Joshi, Prashant P., Syndrome of inappropriate ADH secretion (SIADH) associated with citalopram use. Indian J Psychiatry. 2005 Apr-Jun; 47(2): 119–120. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2918297/

(23) Bouman WP, Pinner G, Johnson H. Incidence of selective serotonin reuptake inhibitor (SSRI) induced hyponatraemia due to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion in the elderly. International Journal of Geriatric Psychiatry. 1998; 13: 12-15. http://www.ncbi.nlm.nih.gov/pubmed/9489575

(24) Medscape SIADH – Physical Examination
http://emedicine.medscape.com/article/246650-clinical#a0256

(25) Meulendijks D, Mannesse CK, Jansen PA, van Marum RJ, Egberts TC. Antipsychotic-induced hyponatraemia: a systematic review of the published evidence. Drug Saf. 2010 Feb 1;33(2):101-14.
http://www.ncbi.nlm.nih.gov/pubmed/20082537

(26) Hyponatraemia A.D.A.M. Illustrated Medical Encyclopedia.
http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001431/

(27) Movig, Kris L. L., “Association between antidepressant drug use and hyponatraemia: a case-control study” Br J Clin Pharmacol. 2002 April; 53(4): 363–369. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1874265/pdf/bcp0053-0363.pdf

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

(29) La Torre, Daria and Falorni, Alberto. Pharmacological causes of hyperprolactinemia Ther Clin Risk Manag. 2007 October; 3(5): 929–951.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2376090/

(30) Vania dos Santos Nunes, César Luiz Boguszewski, Célia Regina Nogueira, Bárbara Corrêa Krug, and Karine Medeiros Amaral, Clinical Practice Guidelines for Pharmaceutical Treatment of Hyperprolactinemia. Ministry of Health Department of Health Care Ordinance no. 208 of 23 April 2010. (Amended 26 May 2010)
http://www.hospitalalemao.org.br/haoc/repositorio/17/documentos/word_biblioteca/375-394-Hiperprolactinemia_ing_revDavid_FINAL.pdf

(31) Cowen PJ, Sargent PA. Changes in plasma prolactin during SSRI treatment: evidence for a delayed increase in 5-HT neurotransmission. J Psychopharmacol. 1997;11(4):345-8. http://www.ncbi.nlm.nih.gov/pubmed/9443523

(32) Emiliano AB, Fudge JL. From galactorrhea to osteopenia: rethinking serotonin-prolactin interactions. Neuropsychopharmacology. 2004 May;29(5):833-46. http://www.nature.com/npp/journal/v29/n5/full/1300412a.html

(33) Clayton AH, Pradko AF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry 2002; 63:357–366. http://altcancerweb.com/bipolar/antidepressants/sexual-dysfunction-newer-antidepressants.pdf 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

(34) Masand PS, Gupta S. Long-term side effects of newer-generation antidepressants: SSRIs, venlafaxine, nefazodone, bupropion, and mirtazapine. Ann Clin Psychiatry 2002; 14:175–182. http://www.ncbi.nlm.nih.gov/pubmed/12585567

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

(35) Wessels-van Middendorp AM, Timmerman L. [Galactorrhoea and the use of selective serotonin reuptake inhibitors]. Tijdschr Psychiatr. 2006;48(3):229-34. Dutch. http://www.ncbi.nlm.nih.gov/pubmed/16956087

(36) Marshall AM, Nommsen-Rivers LA, Hernandez LL, Dewey KG, Chantry CJ, Gregerson KA, Horseman ND. Serotonin transport and metabolism in the mammary gland modulates secretory activation and involution. J Clin Endocrinol Metab. 2010 Feb;95(2):837-46. Epub 2009 Dec 4.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2840848/

(37) Diem, Susan J. MD, MPH, Depression, Antidepressants, and Bone Loss Profiles in Psychiatry: Primary Psychiatry. 2008;15(4):27-29
http://mbldownloads.com/0408PP_Interview_Diem.pdf

(38) Antidepressants and Risk for Osteoporosis, Massachusets General Hospital Center for Womens Mental Health. Published: August 15, 2008
http://www.womensmentalhealth.org/posts/antidepressants-and-risk-for-osteoporosis/

(39) Osteopenia From Wikipedia, the free encyclopedia.
http://en.wikipedia.org/wiki/Osteopenia

(40) Haney EM, Chan BK, Diem SJ, Ensrud KE, Cauley JA, Barrett-Connor E, Orwoll E, Bliziotes MM; for the Osteoporotic Fractures in Men Study Group. "Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men." Arch Intern Med. 2007 Jun 25;167(12):1246-51.
http://www.ncbi.nlm.nih.gov/pubmed/17592097

(41) Robinson, Donald S. MD. Increased Fracture Risk and Psychotropic Medications Primary Psychiatry. 2008;15(10):32-34
http://www.primarypsychiatry.com/aspx/articledetail.aspx?articleid=1778

(42) Bolton JM, Metge C, Lix L, Prior H, Sareen J, Leslie WD. Fracture risk from psychotropic medications: a population-based analysis. J Clin Psychopharmacol. 2008 Aug;28(4):384-91. http://www.ncbi.nlm.nih.gov/pubmed/18626264

(43) Mercola J., "Best-Selling Drug Attacks Your Heart, Brain and Bones"14.4.12 http://articles.mercola.com/sites/articles/archive/2012/04/14/antidepressants-cause-heart-disease.aspx

(44) Richards JB, Papaioannou A, Adachi JD, Joseph L, Whitson HE, Prior JC, Goltzman D; Canadian Multicentre Osteoporosis Study Research Group. Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med. 2007 Jan 22;167(2):188-94. http://www.ncbi.nlm.nih.gov/pubmed/17242321

(45) Ziere G, Dieleman JP, van der Cammen TJ, Hofman A, Pols HA, Stricker BH. Selective serotonin reuptake inhibiting antidepressants are associated with an increased risk of nonvertebral fractures. J Clin Psychopharmacol. 2008 Aug;28(4):411-7. http://www.ncbi.nlm.nih.gov/pubmed/18626268

(46) Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. Lancet. 1998 May 2;351(9112):1303-7. http://www.ncbi.nlm.nih.gov/pubmed/9643791

(47) Hankinson SE, Willett WC, Michaud DS, Manson JE, Colditz GA, Longcope C, Rosner B, Speizer FE. Plasma prolactin levels and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 1999 Apr 7;91(7):629-34. http://www.ncbi.nlm.nih.gov/pubmed/10203283

(48) Kwa HG, Cleton F, Wang DY, Bulbrook RD, Bulstrode JC, Hayward JL, Millis RR, Cuzick J. A prospective study of plasma prolactin levels and subsequent risk of breast cancer. Int J Cancer. 1981 Dec;28(6):673-6. http://www.ncbi.nlm.nih.gov/pubmed/7333701

(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

(50) C. W. Welsch. G. Louks. D. Fox. and C. Brooks, Enhancement by prolactin of carcinogen induced mammary cancerigenesis in the male rat.
Br J Cancer. 1975 October; 32(4): 427–431.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2024771/?tool=pmcentrez

(51) Limas CJ, Kroupis C, Haidaroglou A, Cokkinos DV. Hyperprolactinaemia in patients with heart failure: clinical and immunogenetic correlations. Eur J Clin Invest. 2002 Feb;32(2):74-8.
http://www.ncbi.nlm.nih.gov/pubmed/11895452?dopt=Abstract

(52) Curtarelli G., and C Ferrari C., Cardiomegaly and heart failure in a patient with prolactin-secreting pituitary tumour. Thorax. 1979 June; 34(3): 328–331.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC471069/

(53) Weeke P, Jensen A, Folke F, Gislason GH, et al. Antidepressant use and risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. Clin Pharmacol Ther. 2012 Jul;92(1):72-9. doi: 10.1038/clpt.2011.368. Epub 2012 May 16.
http://www.ncbi.nlm.nih.gov/pubmed/22588605

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

(55) Sala M, Coppa F, Cappucciati C, Brambilla P, d'Allio G, Caverzasi E, Barale F, De Ferrari GM. Antidepressants: their effects on cardiac channels, QT prolongation and Torsade de Pointes. Curr Opin Investig Drugs. 2006 Mar;7(3):256-63. http://www.ncbi.nlm.nih.gov/pubmed/16555686

(56) Rajamani S. et al, Br J Pharmacol. 2006 November; 149(5): 481–489. Published online 2006 September 11. Drug-induced long QT syndrome: hERG K^+ channel block and disruption of protein trafficking by fluoxetine and norfluoxetine http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2014667/

(57) Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, Erb JL, Churchill SE, Kohane IS, Iosifescu DV, Smoller JW, Perlis RH. QT interval and antidepressant use: a cross sectional study of electronic health records. BMJ. 2013 Jan 29;346:f288. http://www.ncbi.nlm.nih.gov/pubmed/23360890

(58) Tata LJ, West J, Smith C, Farrington P, Card T, Smeeth L, Hubbard R. General population based study of the impact of tricyclic and selective serotonin reuptake inhibitor antidepressants on the risk of acute myocardial infarction. Heart. 2005 Apr;91(4):465-71. http://www.ncbi.nlm.nih.gov/pubmed/15772201

(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

(60) Acikel S, Dogan M, Sari M, Kilic H, Akdemir R. Prinzmetal-variant angina in a patient using zolmitriptan and citalopram. Am J Emerg Med. 2010 Feb;28(2):257.e3-6.
http://www.ncbi.nlm.nih.gov/pubmed/20159412

(61) Bo Jian et al., Serotonin Mechanisms in Heart Valve Disease I
Am J Pathol. 2002 December; 161(6): 2111–2121.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1850922/

(62) Lessard E, Yessine MA, Hamelin BA, O'Hara G, LeBlanc J, Turgeon J. Influence of CYP2D6 activity on the disposition and cardiovascular toxicity of the antidepressant agent venlafaxine in humans. http://www.ncbi.nlm.nih.gov/pubmed/10780263?dopt=Abstract&holding=npg

(63) Eker SS, Akkaya C, Ersoy C, Sarandol A, Kirli S. Reversible escitalopram-induced hypothyroidism. Gen Hosp Psychiatry. 2010 Sep-Oct;32(5):559.e5-7. Epub 2010 Apr 27. http://www.ncbi.nlm.nih.gov/pubmed/20851281

(64) Boyer EW, Shannon M. "The serotonin syndrome." N Eng J Med. 2005; 352 (11) p1112-1120. http://www.smbs.buffalo.edu/acb/neuro/readings/SerotoninSyndrome.pdf

(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.

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm124349.htm

(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
http://www.psychotropical.com/index.php/serotonin-toxicity

(67) Bijl D. "The serotonin syndrome". (October 2004) *Neth J Med* 62 (9): 309–13.
http://www.ncbi.nlm.nih.gov/pubmed/15635814

(68) Serotonin Syndrome Choice and Medication. Information for people who use services, carers and professionals.
http://www.choiceandmedication.org/ashtonshospitalpharmacy/pdf/handyfactsheetserotoninsyndrome.pdf

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

(70) J. Bastani, M. Troester and A. Bastani, “Serotonin syndrome and fluvoxamine: A case study.” Nebraska Medical Journal 1996 Apr; 81 (4): 107–109. http://www.ncbi.nlm.nih.gov/pubmed/8628448

(71) Satoh K., Takano S., Onogi T., Ohtsuki K., Kobayashi T., “Serotonin syndrome caused by minimum doses of SSRIS in a patient with spinal cord injury.” Fukushima J Med Sci. 2006 Jun;52(1):29-33. http://www.ncbi.nlm.nih.gov/pubmed/16995352

(72) Pilgrim JL, Gerostamoulos D, Drummer OH. Review: Pharmacogenetic aspects of the effect of cytochrome P450 polymorphisms on serotonergic drug metabolism, response, interactions, and adverse effects. Forensic Sci Med Pathol. 2011 Jun;7(2) : 162-84. Epub 2010 Nov 4. Review. http://www.ncbi.nlm.nih.gov/pubmed/21052868

(73) Sato A, Okura Y, Minagawa S, Ohno Y, Fujita S, Kondo D, Hayashi M, Komura S, Kato K, Hanawa H, Kodama M, Aizawa Y. Life-threatening serotonin syndrome in a patient with chronic heart failure and CYP2D6*1/*5. Mayo Clin Proc. 2004 Nov;79(11):1444-8. http://www.ncbi.nlm.nih.gov/pubmed/15544025

(74) Serotonin syndrome: Triad of symptoms in Serotonin Syndrome/Toxicity Reminder. Information for Health Professionals Prescriber Update 2010; 31(4):30-31 New Zealand Medicines and Medical Devices Safety Authority. 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] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm085845.htm

(77) Mackay FJ, Dunn NR, Mann RD, Antidepressants and the serotonin syndrome in general practice. Br J Gen Pract. 1999 Nov;49(448):871-4. [abstract] http://www.ncbi.nlm.nih.gov/pubmed/10818650?dopt=Abstract

(78) Robinson, DS. MD "Serotonin Syndrome" Psychopharmacology Research Tutorial for Practitioners. Primary Psychiatry. 2006;13(8):36-38 http://mbldownloads.com/0806PP_Robinson.pdf

(79) Kessing LV, Søndergård L, Forman JL, Andersen PK. "Antidepressants and dementia." J Affect Disord. 2009 Sep;117(1-2):24-9. Epub 2009 Jan 12. http://www.ncbi.nlm.nih.gov/pubmed/19138799 Source: Jackson, Grace E. MD. (2009), *"Drug-Induced Dementia a Perfect Crime"* Bloomington, IN: Author House. p. 67

(80) Chen Y, Guo JJ, Li H, Wulsin L, Patel NC. "Risk of cerebrovascular events associated with antidepressant use in patients with depression: a population-based, nested case-control study." Ann Pharmacother. 2008 Feb;42(2):177-84. http://www.ncbi.nlm.nih.gov/pubmed/18212255 Source: Jackson, Grace E. MD. (2009), *"Drug-Induced Dementia a Perfect Crime"* Bloomington, IN: Author House. p. 63

(81) Brandt-Christensen M, Kvist K, Nilsson FM, Andersen PK, Kessing LV. "Treatment with antidepressants and lithium is associated with increased risk of treatment with antiparkinson drugs: a pharmacoepidemiological study." J Neurol Neurosurg Psychiatry. 2006 Jun;77(6):781-3.
http://www.ncbi.nlm.nih.gov/pubmed/16705201
Source: Jackson, Grace E. MD. (2009), *"Drug-Induced Dementia a Perfect Crime"* Bloomington, IN: Author House. p.60

(82) Pies, Ronald W. MD Must We Now Consider SRIs Neuroleptics? Journal of Clinical Psychopharmacology: December 1997 - Volume 17 - Issue 6 - pp 443-445. Guest Editorial.
http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&ved=0CCMQFjAA&url=http%3A%2F%2Fwww.lykkepiller.info%2Fgfx%2FJournal%2520of%2520Clinical%2520Psychopharmacology.doc&ei=EQJOUJyFIOiq0QWrz4CoCA&usg=AFQjCNEcZEer2a0UomqCA-2RUZ-JHpdViQ
Source: Jackson Grace E. MD (2005) *"Rethinking Psychiatric Drugs: A Guide for Informed Consent"*. Bloomington, IN: Author House. p.126

(83) Caley CF. Extrapyramidal reactions and the selective serotonin-reuptake inhibitors. Ann Pharmacother. 1997 Dec;31(12):1481-9. Review.
http://www.ncbi.nlm.nih.gov/pubmed/9416386

(84) Gerber PE. Lynd LD., Selective serotonin-reuptake inhibitor-induced movement disorders Ann Pharmacother June 1, 1998 32:692-698
http://www.theannals.com/content/32/6/692.short

(85) Leo RJ. Movement disorders associated with the serotonin selective reuptake inhibitors J Clin Psychiatry 1996;57:449-54.
http://psychrights.org/research/Digest/AntiDepressants/DrJackson/Leo1996.pdf

(86) Lane, RM. “SSRI-induced extrapyramidal side-effects and akathisia: Implications for treatment”, Journal of Psychopharmacology 12 (1998), 192–214.
http://www.ncbi.nlm.nih.gov/pubmed/9694033

(87) Gill HS, DeVane CL, Risch SC. Extrapyramidal symptoms associated with cyclic antidepressant treatment: a review of the literature and consolidating hypotheses. J Clin Psychopharmacol. 1997;17(5):377–89.
http://www.ncbi.nlm.nih.gov/pubmed/9315989

(88) APA Textbook of Psychopharmacology: "*Akathisia, however, is the most common neurological symptom caused by SSRIs*." Edited by Schatzberg and Nemeroff Second Edition, 1998, p.939

(89) Barnes TRE., A Rating Scale for Drug-Induced Akathisia
British Journal of Psychiatry (1989), 154, 672 - 676
http://egret.psychol.cam.ac.uk/medicine/scales/Barnes_1989_akathisia.pdf

(90) Gibb WRG., Lees AJ., The clinical phenomenon of akathisia. Journal of Neurology, Neurosurgery, and Psychiatry 1986;49:861-866
http://jnnp.bmj.com/content/49/8/861.full.pdf

(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.nice.org.uk/nicemedia/live/12329/45896/45896.pdf

(92) Ciraulo, Domenic A., et al., "Clinical Pharmacology and Therapeutics of Antidepressants" D.A. Ciraulo and R.I. Shader (eds.), Pharmacotherapy of Depression DOI 10.1007/978-1-60327-435-7_2, c Springer Science+Business Media, LLC 2011 http://www.springer.com/cda/content/document/cda_downloaddocument/9781603274340-c1.pdf?SGWID%3

(93) Rothschild AJ, Locke CA. Re-exposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. J Clin Psychiatry. 1991 Dec; 52 (12): 491-3. http://www.ncbi.nlm.nih.gov/pubmed/1752848

(94) Healy D. Lines of evidence on the risks of suicide with selective serotonin reuptake inhibitors. Psychother Psychosom. 2003 Mar-Apr;72(2):71-9. http://www.ncbi.nlm.nih.gov/pubmed?term=12601224

(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/

(96) Glenmullen, J. (2000) *Prozac Backlash: overcoming the dangers of Prozac, Zoloft, Paxil, and other antidepressants with safe, effective alternatives.* Simon & Schuster. http://www.antidepressantsfacts.com/prozac-lilly-50.000-suicides-archive.htm

(97) Cohen JS MD., Suicides and Homicides in Patients Taking Paxil, Prozac, and Zoloft: Why They Keep Happening -- And Why They Will Continue. Underlying Causes That Continue to Be Ignored by Mainstream Medicine and the Media. The MedicationSense E-Newsletter, www.MedicationSense.com. http://www.medicationsense.com/articles/oct_dec_03/suicides_homicides.html

(98) Raja M, Azzoni A, Lubich L. "Aggressive and violent behavior in a population of psychiatric inpatients." Soc Psychiatry Psychiatr Epidemiol. 1997 Oct;32(7):428-34. http://www.ncbi.nlm.nih.gov/pubmed/9383975

(99) Pringle E. “SSRI-Induced Akathisia's Link To Suicide and Violence” Lawyers and Settlements.com August 18, 2007, 09:00:00AM.
http://www.lawyersandsettlements.com/features/drugs-medical/ssri-suicide-akathisia.html#.UJp614ZoWSo

(100) Jackson, Grace E. MD. (2005), *"Rethinking Psychiatric Drugs: A Guide for Informed Consent"* Bloomington, IN: Author House. Page 117
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

(102) Lucire Y, Crotty C. Antidepressant-induced akathisia-related homicides associated with diminishing mutations in metabolizing genes of the CYP450 family. August 2011 Volume 2011:4 Pages 65 – 81
http://www.dovepress.com/getfile.php?fileID=10671

(103) Roy H Perlis, David Mischoulon, Jordan W Smoller, Yu-Jui Yvonne Wan, Stefania Lamon-Fava, Keh-Ming Lin, Jerrold F Rosenbaum, Maurizio Fava. Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. Biological Psychiatry – 1 November 2003 (Vol. 54, Issue 9, Pages 879-883.
http://www.biologicalpsychiatryjournal.com/article/S0006-3223%2803%2900424-4/abstract

(104) The Dystonia Society – Tardive Dystonia
http://www.dystonia.org.uk/pdf/Tardive.pdf

(105) Schneider, D. MD and Ravin, Paula D MD, 'Dystonia, Tardive' Overview in Medscape Clinical Reference Updated: Apr 2, 2010
http://emedicine.medscape.com/article/287230-overview

(106) Madhusoodanan S, Alexeenko L, Sanders R, Brenner R. "Extrapyramidal symptoms associated with antidepressants--a review of the literature and an analysis of spontaneous reports". Ann Clin Psychiatry. 2010 Aug;22(3):148-56. Review.
http://www.aacp.com/pdf%2F0810%2F0810ACP_Madhusoodanan.pdf

(107) García-Parajuá P, de Ugarte L, Baca E. More data for the CYP2D6 hypothesis? The in vivo inhibition of CYP2D6 isoenzyme and extrapyramidal symptoms induced by antidepressants in the elderly. J Clin Psychopharmacol. 2004;24:111-112.
http://www.ncbi.nlm.nih.gov/pubmed/14709967?dopt=AbstractPlus
Source: Madhusoodanan S, Alexeenko L, Sanders R, Brenner R. "Extrapyramidal symptoms associated with antidepressants--a review of the literature and an analysis of spontaneous reports". Ann Clin Psychiatry. 2010 Aug;22(3):148-56. Review.
http://www.aacp.com/pdf%2F0810%2F0810ACP_Madhusoodanan.pdf

(108) Vandel P, Haffen E, Vandel S, Bonin B, Nezelof S, Sechter D, Broly F, Bizouard P, Dalery J. Drug extrapyramidal side effects. CYP2D6 genotypes and phenotypes. Eur J Clin Pharmacol. 1999 Nov;55(9):659-65.
http://www.ncbi.nlm.nih.gov/pubmed/10638395
Source: Madhusoodanan S, Alexeenko L, Sanders R, Brenner R. "Extrapyramidal symptoms associated with antidepressants--a review of the literature and an analysis of spontaneous reports". Ann Clin Psychiatry. 2010 Aug;22(3):148-56. Review.
http://www.aacp.com/pdf%2F0810%2F0810ACP_Madhusoodanan.pdf

(109) Connolly A. Race and prescribing. The Psychiatrist Online May 2010 34:169-171 http://pb.rcpsych.org/content/34/5/169.full

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

(111) Spigset O. Adverse reactions of selective serotonin reuptake inhibitors: reports from a spontaneous reporting system. Drug Saf. 1999 Mar;20(3):277-87. http://www.ncbi.nlm.nih.gov/pubmed/10221856

(112) Anderson, Lily B. et al "Effects of selective serotonin reuptake inhibitors on motor neuron survival" International Journal of General Medicine May 2009 Volume 2009:2 Pages 109 – 115 http://www.dovepress.com/getfile.php?fileID=4844

(113) National Institute of Neurological Disorders and Stroke (NINDS) Tardive Dyskinesia Information Page http://www.ninds.nih.gov/disorders/tardive/tardive.htm

(114) Oesterheld JR. 2D6. In *Clinical Manual of Drug Interaction. Principles for Medical Practice* (eds GH Wynn, JR Oesterheld, KL Cozza, SC Armstrong): *77*-98. American Psychiatric Publishing, 2009.
Source: Connolly A. Race and prescribing. The Psychiatrist Online May 2010 34: 169-171 http://pb.rcpsych.org/content/34/5/169.full

(115) Dubovsky SL, Thomas M. Tardive dyskinesia associated with fluoxetine. Psychiatr Serv. 1996 Sep;47(9):991-3.
http://www.ncbi.nlm.nih.gov/pubmed/8875667

(116) Fitzgerald K. and Healy D. Dystonias and Dyskinesias of the Jaw Associated with the Use of SSRIs. Human Psychopharmacology, Vol. 10,215-219 (1995)
http://davidhealy.org/wp-content/uploads/2012/05/1995-Dystonias-and-dyskinesias-of-the-jaw.pdf

(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

(118) Altindag A, Yanik M, Asoglu M. The emergence of tics during escitalopram and sertraline treatment. Int Clin Psychopharmacol. 2005 May;20(3):177-8. http://www.ncbi.nlm.nih.gov/pubmed/15812270

(119) Czéh B, Simon M, Schmelting B, Hiemke C, Fuchs E. Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. Neuropsychopharmacology. 2006 Aug;31(8):1616-26. Epub 2005 Dec 14. http://www.ncbi.nlm.nih.gov/pubmed/16395301
Source: Jackson, Grace E. MD. (2009), *"Drug-Induced Dementia a Perfect Crime"* Bloomington, IN: Author House. p. 111

(120) Sairanen M, Lucas G, Ernfors P, Castrén M, Castrén E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. J Neurosci. 2005 Feb 2;25(5):1089-94. http://www.ncbi.nlm.nih.gov/pubmed/15689544
Source: Jackson, Grace E. MD. (2009), *"Drug-Induced Dementia a Perfect Crime"* Bloomington, IN: Author House. p. 121

(121) Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A. 1996 Apr 30;93(9):3908-13. http://www.ncbi.nlm.nih.gov/pubmed/8632988
Source: Jackson, Grace E. MD. (2009), *"Drug-Induced Dementia a Perfect Crime"* Bloomington, IN: Author House. p. 129

(122) Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. Am J Psychiatry. 2000 Jan;157(1):115-8. http://www.ncbi.nlm.nih.gov/pubmed/10618023
Source: Jackson, Grace E. MD. (2009), *"Drug-Induced Dementia a Perfect Crime"* Bloomington, IN: Author House. p. 130

(123) Deepak Kumar et al, Upper gastrointestinal bleeding in a patient with depression receiving selective serotonin reuptake inhibitor therapy. Indian J Pharmacol. 2009 February; 41(1): 51–53.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2825017/?tool=pmcentrez

(124) Dalton SO, Johansen C, Mellemkjaer L, Nørgård B, Sørensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Arch Intern Med. 2003 Jan 13;163(1):59-64. http://www.ncbi.nlm.nih.gov/pubmed/12523917

(125) Alain Li Wan Po, Antidepressants and upper gastrointestinal bleeding, BMJ. 1999 October 23; 319(7217): 1081–1082. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1116881/

(126) Victor M Castro et al. "Incident user cohort study of risk for gastrointestinal bleed and stroke in individuals with major depressive disorder treated with antidepressants." BMJ Open 2012;2 Pharmacology and therapeutics. http://bmjopen.bmj.com/content/2/2/e000544.full.pdf+html

(127) Pisani F, Oteri G, Costa C, Di Raimondo G, Di Perri R. Effects of psychotropic drugs on seizure threshold. Drug Saf. 2002;25(2):91-110. http://www.ncbi.nlm.nih.gov/pubmed/11888352

(128) Haddad PM, Dursun SM. Neurological complications of psychiatric drugs: clinical features and management. Hum Psychopharmacol. 2008 Jan;23 Suppl 1:15-26. http://www.ncbi.nlm.nih.gov/pubmed/18098217

(129) Spigset O, Hedenmalm K, Dahl ML, Wiholm BE, Dahlqvist R. Seizures and myoclonus associated with antidepressant treatment: assessment of potential risk factors, including CYP2D6 and CYP2C19 polymorphisms, and treatment with CYP2D6 inhibitors. Acta Psychiatr Scand 1997;Nov;96(5):379-84. http://www.ncbi.nlm.nih.gov/pubmed/9395157?dopt=Abstract&holding=npg

(130) Costagliola C, Parmeggiani F, Sebastiani A. "SSRIs and intraocular pressure modifications: evidence, therapeutic implications and possible mechanisms." CNS Drugs. 2004;18(8):475-84. http://www.ncbi.nlm.nih.gov/pubmed/15182218

(131) Richa S, Yazbek JC. Ocular adverse effects of common psychotropic agents: a review. CNS Drugs. 2010 Jun;24(6):501-26. http://www.ncbi.nlm.nih.gov/pubmed/20443647

(132) Costagliola C., et al.,“Selective Serotonin Reuptake Inhibitors: A Review of its Effects on Intraocular Pressure”.Curr Neuropharmacol. 2008 December; 6(4): 293-310. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2701282/?tool=pmcentrez

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

(134) Benzer TI, MD, PhD, et al, (2010) ‘Neuroleptic Malignant Syndrome in Emergency Medicine.’ Source: Medscape. Overview: Epidemiology http://emedicine.medscape.com/article/816018-overview#a0199

(135) Schibuk M, Schachter D. A role for catecholamines in the pathogenesis of neuroleptic malignant syndrome. Can J Psychiatry. 1986 Feb;31(1):66-9. PubMed PMID: 3948109.http://www.ncbi.nlm.nih.gov/pubmed/3948109

(136) Jussi Honkola, Eeva Hookana, Sanna Malinen. Kari S. Kaikkonen, M. Juhani Junttila, Matti Isohanni, Marja-Leena Kortelainen, Heikki V. Huikuri Psychotropic medications and the risk of sudden cardiac death during an acute coronary event European Heart J *(2011)* First published online: September 14, 2011 http://eurheartj.oxfordjournals.org/content/early/2011/09/14/eurheartj.ehr368.abstract

(137) Kelly, Catherine M. et al., "Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study" British Medical Journal, February 8, 2010. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2817754/

(138) Kaneda Y, Kawamura I, Fujii A, Ohmori T. Serotonin syndrome — 'potential' role of the **CYP2D6** genetic polymorphism in Asians. Int J Neuropsychopharmacol 2002; 5:105-6. http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=100593 Source: Boyer EW, Shannon M. "The serotonin syndrome." N Eng J Med. 2005; 352 (11) p1112-1120. http://www.smbs.buffalo.edu/acb/neuro/readings/SerotoninSyndrome.pdf

(139) Mitchell PB. Drug interactions of clinical significance with selective serotonin reuptake inhibitors. Drug Saf 1997;17:390-406. http://europepmc.org/abstract/MED/9429838
Source: Boyer EW, Shannon M. "The serotonin syndrome." N Eng J Med. 2005; 352 (11) p1112-1120. http://www.smbs.buffalo.edu/acb/neuro/readings/SerotoninSyndrome.pdf

(140) Domar AD., Moragianni VA., Ryley DA. and Urato AC. The risks of selective serotonin reuptake inhibitor use in infertile women: a review of the impact on fertility, pregnancy, neonatal health and beyond. Human Reproduction, Vol.0, No.0 pp. 1–12, October 31, 2012
http://humrep.oxfordjournals.org/content/early/2012/10/31/humrep.des383.full

(141) Antidepressants Linked to Miscarriage Risk
Researchers See Possible Connection Between SSRIs and Miscarriages
By Katrina Woznicki, WebMD Health News, Reviewed by Laura J. Martin, MD
http://www.webmd.com/depression/news/20100602/antidepressants-linked-to-miscarriage-risk

(142) Miscarriage/Pregnancy Loss - Study Finds SSRI Antidepressants Link to Increased Miscarriage Risk. Krissi Danielsson, About.com Guide June 2, 2010
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

(144) Mulder EJ, Ververs FF, de Heus R, Visser GH. Selective serotonin reuptake inhibitors affect neurobehavioral development in the human fetus. Neuropsychopharmacology. 2011 Sep;36(10):1961-71. doi: 10.1038/npp.2011.67. Epub 2011 Apr 27. http://www.ncbi.nlm.nih.gov/pubmed/21525859

(145) Alwan S., Reefhuis J., Rasmussen SA., Olney RS., Friedman, JM.
Use of Selective Serotonin-Reuptake Inhibitors in Pregnancy and the Risk of Birth Defects. June 28, 2007 New England Journal of Medicine 2684-2692 V356
http://www.nejm.org/doi/full/10.1056/NEJMoa066584

(146) Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. Pediatrics. 2004 Feb;113(2):368-75. http://www.ncbi.nlm.nih.gov/pubmed/14754951

(147) Dubnov-Raz G, Juurlink DN, Fogelman R, Merlob P, Ito S, Koren G, Finkelstein Y. Antenatal use of selective serotonin-reuptake inhibitors and QT interval prolongation in newborns. Pediatrics. 2008 Sep;122(3):e710-5. http://www.ncbi.nlm.nih.gov/pubmed/18762507

(148) QT Interval from Wikipedia http://en.wikipedia.org/wiki/QT_interval

(149) Duijvestijn YC, Kalmeijer MD, Passier AL, Dahlem P, Smiers F. Neonatal intraventricular haemorrhage associated with maternal use of paroxetine. Br J Clin Pharmacol. 2003 Nov;56(5):581-2. http://www.ncbi.nlm.nih.gov/pubmed/14651736

(150) Salvia-Roigés MD, Garcia L, Goncé-Mellgren A, Esqué-Ruiz MT, Figueras-Aloy J, Carbonell-Estrany X. [Neonatal convulsions and subarachnoid hemorrhage after in utero exposure to paroxetine]. Rev Neurol. 2003 Apr 16-30;36(8):724-6. http://www.ncbi.nlm.nih.gov/pubmed/12717649

(151) Hayes RM, Wu P, Shelton RC, Cooper WO, Dupont WD, Mitchel E, Hartert TV. Maternal antidepressant use and adverse outcomes: a cohort study of 228,876 pregnancies. Am J Obstet Gynecol. 2012 Jul;207(1):49.e1-9. Epub 2012 Apr 30. http://www.ncbi.nlm.nih.gov/pubmed/22727349

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

(153) Australian Adverse Drug Reactions Bulletin, Vol 22, No 4 August 2003 Maternal SSRI use and neonatal effects.
http://www.tga.gov.au/hp/aadrb-0308.htm#a1

(154) Chambers CD, Anderson PO, Thomas RG, Dick LM, Felix RJ, Johnson KA, Jones KL. Weight gain in infants breastfed by mothers who take fluoxetine. Pediatrics. 1999 Nov;104(5):e61.
http://www.ncbi.nlm.nih.gov/pubmed/10545587

(155) Croen LA, Grether JK, Yoshida CK, Odouli R, Hendrick V. Antidepressant Use During Pregnancy and Childhood Autism Spectrum Disorders. *Arch Gen Psychiatry.* 2011;68(11):1104-1112.
http://archpsyc.jamanetwork.com/article.aspx?articleid=1107329

(156) Vlaminck JJ, van Vliet IM, Zitman FG. [Withdrawal symptoms of antidepressants]. Ned Tijdschr Geneeskd. 2005 Mar 26;149(13):698-701. Review. Dutch. http://www.ncbi.nlm.nih.gov/pubmed/15819135

(157) de Moor RA, Mourad L, ter Haar J, Egberts AC. [Withdrawal symptoms in a neonate following exposure to venlafaxine during pregnancy]. Ned Tijdschr Geneeskd. 2003 Jul 12;147(28):1370-2. Dutch.
http://www.ncbi.nlm.nih.gov/pubmed/12892015

(158) Canada Health advisory. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns. August 9, 2004 http://www.antidepressantsfacts.com/2004-08-09-HealthCan-SSRIs-newborns.htm

(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

(160) Haddad PM, Pal BR, Clarke P, Wieck A, Sridhiran S. Neonatal symptoms following maternal paroxetine treatment: serotonin toxicity or paroxetine discontinuation syndrome? J Psychopharmacol. 2005 Sep;19(5):554-7. http://www.ncbi.nlm.nih.gov/pubmed/16166193

(161) Laine K, Heikkinen T, Ekblad U, Kero P. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. Arch Gen Psychiatry. 2003 Jul;60(7):720-6. http://www.ncbi.nlm.nih.gov/pubmed/12860776

(162) Rampono J, Proud S, Hackett LP, Kristensen JH, Ilett KF. A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. Int J Neuropsychopharmacol. 2004 Sep;7(3):329-34. Epub 2004 Mar 22. http://www.ncbi.nlm.nih.gov/pubmed/15035694

(163) Fava GA, Offidani E "The mechanisms of tolerance in antidepressant action." Prog Neuropsychopharmacol Biol Psychiatry. 2010 Aug 20. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/20728491

(164) Kora K, Kaplan P. "Hypomania/mania induced by cessation of antidepressant drugs" Turk Psikiyatri Derg. 2008 Fall;19(3):329-33. Turkish. http://www.ncbi.nlm.nih.gov/pubmed/18791886

(165) Wolfe, RM., Antidepressant withdrawal reactions, *American Family Physician*, August 1997, **56** (2) p.455-462 http://www.ncbi.nlm.nih.gov/pubmed/9262526

(166) Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol. 1996 Oct;16(5):356-62. PubMed PMID: 8889907. http://www.ncbi.nlm.nih.gov/pubmed/8889907

(167) Warner CH. et al Antidepressant Discontinuation Syndrome Am Fam Physician. 2006 Aug 1;74(3):449-456. http://www.aafp.org/afp/2006/0801/p449.html

(168) Tint A, Haddad PM, Anderson IM. The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study. J Psychopharmacol. 2008 May;22(3):330-2. Erratum in: J Psychopharmacol. 2009 Nov;23(8):1006. http://www.ncbi.nlm.nih.gov/pubmed/18515448

(169) ICFDA Adverse SSRI Reactions An ICFDA Closer look
Source: "*Prozac: Panacea or Pandora?"*, Ann Blake Tracy, PH.D.
http://www.antidepressantsfacts.com/tracy-p-450-cortisol.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

(172) Moore M et al “Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database.”BMJ; 339: b3999, 15 Oct 2009
http://www.bmj.com/content/339/bmj.b3999

(173) Pitchot W, Scantamburlo G, Pinto E, Ansseau M. [Discontinuation syndrome associated with antidepressants]. Rev Med Liege. 2007 Oct;62(10):624-7. French.
http://www.ncbi.nlm.nih.gov/pubmed/18069574

(174) Lejoyeux M, Adès J. Antidepressant discontinuation: a review of the literature. J Clin Psychiatry. 1997;58 Suppl 7:11-5; discussion 16. Review.
http://www.ncbi.nlm.nih.gov/pubmed/9219488

(175) Rosenbaum JF, Zajecka J. Clinical management of antidepressant discontinuation. J Clin Psychiatry. 1997;58 Suppl 7:37-40. Review.
http://www.ncbi.nlm.nih.gov/pubmed/9219493

(176) Perahia DG, Kajdasz DK, Desaiah D, Haddad PM. Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder. J Affect Disord. 2005 Dec;89(1-3):207-12. Epub 2005 Nov 2. http://www.ncbi.nlm.nih.gov/pubmed/16266753

(177) Zajecka J, Tracy KA, Mitchell S. Discontinuation symptoms after treatment with serotonin reuptake inhibitors: a literature review. J Clin Psychiatry. 1997 Jul;58(7):291-7. http://www.ncbi.nlm.nih.gov/pubmed/9269249

(178) Schatzberg AF, Haddad P, Kaplan EM, Lejoyeux M, Rosenbaum JF, Young AH, Zajecka J. Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. Discontinuation Consensus panel. J Clin Psychiatry. 1997;58 Suppl 7:5-10. http://www.ncbi.nlm.nih.gov/pubmed/9219487

(179) Breggin Peter R. "Suicidality, violence and mania caused by selective serotonin reuptake inhibitors (SSRIs): A review and analysis" International Journal of Risk & Safety in Medicine 16 (2003/2004) 31–49 http://www.breggin.com/31-49.pdf

Contributors:

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

February 2013