Antidepressant Psychological and Cognitive Adverse Drug Reactions

Preface

Overall mainstream literature does not provide data about antidepressant psychological and cognitive adverse reactions to which some patients' are susceptible.

This document provides relevant antidepressant research information to address this deficit thereby promoting increased awareness for mental health and social care practitioners.

The NICE Guideline for Depression[1] appears to have preference for Serotonin Selective Reuptake Inhibitor (SSRI) antidepressant medication to be the drug of choice in treating mild to severe depression. SSRIs are also prescribed for Generalised Anxiety Disorder, Panic Disorder, Post Traumatic Stress Disorder, Obsessive Compulsive Disorder and Social Phobia.[2]

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Adverse Drug Reactions or “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 the result of drug toxicities accumulated in the body which cause **Adverse Drug Reactions (ADR).**

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.

Antidepressants and Pharmacogenetics

Genetic polymorphisms or variations of drug transporters have been shown to influence drug response[3] and determine susceptibility to adverse drug reactions. This predetermined rate of metabolism is known as **Pharmacogenetics.**

Antidepressant metabolism is complex and drug transporters such as Serotonin Transporter Gene (SERT), CYP450 2D6 and CYP450 2C19 pathways play important roles.[4]

When people have inborn slower rates of metabolism i.e. CYP450 Poor Metaboliser or Intermediate Metaboliser Genotype profiles, or SERT allele variations, antidepressant neuro-toxicities accumulate resulting in adverse reactions.

"Genetic factors contribute for about 50% of the AD (antidepressant) response."[5] The lack of antidepressant therapeutic response together with the emergence of negative emotional disturbances such as suicidal ideation[6, 7] mania and psychosis[8] which some people experience with antidepressant treatment is most likely due to a genetic inability to metabolise medication efficiently.

Neurotransmitters

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.

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

Since many neurotransmitters play important roles in psychological and cognitive well being, it is inevitable unnatural interference by the use of antidepressants will induce psychological and cognitive adverse reactions because every function will be affected.

Antidepressants and Neurotransmitters

SSRIs affect the serotonin neurotransmitter by binding to the serotonin reuptake transporter (SERT) and preventing the normal regulation of serotonin transmitted across the synapse.

Short-term treatment initially causes an increase of serotonin, followed by a decrease due to the regulatory feed back mechanism. Subsequent increase of serotonin occurs several weeks later.[9]

Long-term antidepressant treatment results in the depletion of brain chemicals i.e. serotonin and norepinephrine, which is supported consistently by many studies with animals subjected to SSRI drugs.[9]

Other neurotransmitters and receptors in the brain which SSRIs indirectly influence[9] are dopamine, histamine, adrenaline and acetylcholine.[10]

Serotonin and Acetylcholine Neurotransmitter Functions

Serotonin:

- Cognition - thought, attention, concentration, learning and memory[11]
- Affect - feeling, mood and emotions
- Alertness[12]
- Wakefulness and sleep
- Pain perception[13]

Acetylcholine:

- Cognition - thought, attention, concentration, learning and long-term memory processing.
- Affect - feeling, mood and emotions[12]
- Alertness[14]
- Arousal
- Motivation

Both Serotonin and Acetylcholine play important roles during dreaming.

Dopamine Neurotransmitter Functions

Dopamine:

- Cognition - thinking, attention, learning and memory
- Affect - feeling, mood and emotions
- Sensation of pleasure
- Sexual desire
- Behaviour - compulsions, stereotypies, addictions and desires[9]
- Motivation
- Attachment
- Altruism - unselfish concern for others
- Positive reinforcement - reward
- Focusing, and problem solving[12, 15]

Noradrenaline Neurotransmitter Functions

Noradrenaline:

- Levels of arousal
- Fight or flight
- Concentration[14]
- Sustained focused attention[14]
- Affect - feeling, mood, emotions.
- Forming memories and learning[12]

Optimal levels of noradrenaline provide clear thinking and alertness.[14]

Antidepressants and Neurotransmitter Disruption

"Contrary to prevailing beliefs and published deception, the treatments which are widely prescribed to patients in an effort to relieve depression appear to reduce, rather than enhance, the synthesis, release, and/or target sensitivity of the neurotransmitters which are presumed to be responsible for healthy mood"[16]

Neurotransmitter disruption resulting from antidepressant therapy probably accounts for an unhealthy mood as antidepressants have "… the potential to provoke a wide variety of psychiatric symptoms, including mania, paranoia, hallucinations, panic attacks, or obsessive ruminations - all of which may contribute to suicidal and/or homicidal behaviour."[9]

Antidepressants and Neurotransmitter Disruption

Antidepressant drugs' disruption of the brain's processes have been associated with negative psychological effects which are encapsulated by the following experts:

Prof. David Healy observes "Many people taking SSRIs,…. have reported uncharacteristic feelings of violence and suicidal thoughts and actions and these seem to be particularly associated with changes in dose."[17]

Grace Jackson MD. observes "…suicidality, low mood anxiety, fatigue, anergia or sleep disturbance may occur when drug levels fall or stop."[9]

Practitioners need to be aware patients are more vulnerable to psychological effects when there are antidepressant prescription changes.

Antidepressant Neurotransmitter Disruption

Antidepressant neurotransmitter disruption can cause the following psychological and cognitive effects, which are in essence adverse drug reactions:

Affective	**Cognitive**	**Psychosis**
Hypomania Impulsivity Violence and aggression Mood disorders/swings Aggravated Depression Anxiety/Agitation Nervousness/Irritability Impatience /feeling edgy Panic Attacks Inner restlessness - Akathisia	Suicidality Apathy and Emotional blunting Obsessive & Intrusive thoughts Confusion/memory impairment Disinhibition Fears and Phobias	Mania Psychosis/hallucinations Altered personality and disturbed behaviour Deliriousness **Sleep** Insomnia Vivid or strange disturbing dreams

Refs: 18 – 21.

Vulnerability to Long Term Depression

Dozens of studies, spanning more than 30 years research have demonstrated that serotonin drugs i.e. **Serotonin Selective Reuptake Inhibitors (SSRIs)** create a lasting vulnerability to depressed mood via the serotonin system. Similarly this outcome is replicated with norepinephrine antidepressants drugs. i.e. **Selective Norephineprine Reuptake Inhibitors (SNRIs)**[9]

"Notably formerly depressed individuals who have received treatment with psychotherapy - but who have avoided pharmaceuticals - have not displayed this reaction when subjected to the same method of dietary manipulation (monoamine depletion)."[22-24]

Vulnerability to Long Term Depression

The Acute Tryptophan Depletion Test:

This dietary manipulation test proves antidepressants cause disruption of Serotonin and Norepinephrine circuits, leaving a "vulnerability to recurrent major depression." [9]

In the test serotonin levels are abruptly depleted by consumption of a high amino-acid drink devoid of the essential amino acid tryptophan, the precursor of serotonin.

Additionally alpha-methyl-para-tyrosine is administered in order to inhibit production of norepinephrine and dopamine.[9]

Vulnerability to Long Term Depression

Results of the Acute Tryptophan Depletion Test:

Healthy subjects experience no depressed feelings in response to acute reductions in serotonin, dopamine and norepinephrine.

Unmedicated, currently depressed subjects did not experience a worsening of symptoms.

Recently remitted patients i.e. medicated, exposed to neurotransmitter depletion experienced a rapid return of symptoms.

Previously medicated, fully recovered patients, (median 30 weeks), exposed to serotonin depletion experienced a worsening of symptoms which was on average 8 points on the Hamilton Depression Rating Scale.[9]

Vulnerability to Long Term Depression

Conclusion of the Acute Tryptophan Depletion Test:

"…approximately **60-80% of formerly medicated patients experience a rapid return of depressive symptoms** which corresponds to the target of past treatment (serotonin drugs persistently disrupt the serotonin circuits; norepinephrine drugs persistently disrupt the norepinephrine circuits)." [16]

Patients who experience psychotherapy without antidepressant treatment do not experience a return of depressive symptoms.

Patients who have never used antidepressants do not experience a worsening of depressive symptoms.

This research makes it clear antidepressant medications cause permanent vulnerability to depression despite helpful psychotherapy.

Treatment Resistant Depression - Tardive Dysphoria

In the early 1990s only about 10% to 15% of patients with major depressive illness had treatment-resistant depression (and thus were chronically ill.) In 2006, when SSRI use greatly increased, researchers reported that nearly **40%** of patients were now treatment-resistant.[25]

Up to 80% of patients maintained on an antidepressant long-term suffer a recurrence of symptoms.[25]

In some individuals, even those who have had a positive initial response, persistent use of antidepressants may cause Tardive Dysphoria - chronic depressive state - due to anatomical changes taking place in the serotonin system in response to serotonin reuptake inhibition.[25]

Younger age at onset of antidepressant exposure and individuals with genetic under expression of the serotonin transporter, such as with the short form of the serotonin transporter, may have increased risk of Tardive Dysphoria.[25]

Serotonin Syndrome

Serotonin Syndrome psychological status changes are part of the triad of clinical symptoms that includes autonomic instability and neuro-muscular abnormalities due to excessive serotonin levels.[26, 27]

Psychological and Cognitive Changes:

- Confusion
- Agitation
- Akathisia/Restlessness
- Memory loss
- Coma
- Dizziness
- Hallucinations
- Hypomania
- Anxiety

Refs: 18-28.

Anxiety and akathesia may be attributed to the patient as opposed to [26] Serotonin Syndrome which is potentially a fatal condition.[27]

Akathisia

"Akathisia is a painful inner agitation that typically manifests as the inability to sit still or to stop moving. The hyperactivity may manifest itself subtly as a feeling of jitteriness or grossly as frantic pacing or repeatedly sitting up and down. The inner agitation associated with akathisia can become extremely uncomfortable, causing the individual to feel tortured from within." [19]

Akathisia is associated with suicide, [29-35] aggression and violence.[36- 39]

Akathisia

Akathisia is linked with SSRIs[40-42] and is the most common SSRI induced neurological symptom.[43] Serotonergic over stimulation (serotonin toxicity), genetic CYP450 diminished drug elimination genotype[39] and SSRIs effect on dopamine cell activity,[44] which is backed up with animal research,[45] have all been attributed as potential triggers for akathisia.[40]

Media coverage by BBC Panorama programme "Secrets of Seroxat"[46] in 2002, turned the drug companies' denial of SSRI Seroxat induced akathisia into an acceptance of a potential drug effect and additionally was included in the Patient Information Leaflet in 2003.

CYP450 2D6, 2C19 and 2C9 variants[39] and the short allele of the serotonin transporter gene-linked polymorphic region (5HTTLPR) are associated with akathesia.[47]

Suicide

Not only research and case studies document the association of self harm with SSRIs,[48] there are strong links between SSRI antidepressant drugs and suicide,[49-51] being more common in SSRI treatment compared with tricyclic antidepressant treatment.[52]

Statistics from an extensive report[53] about suicides committed in Sweden depict:

- 39% (488) of patients committed suicide having taken antidepressants 180 days prior to the event.
- Of the 377 women who committed suicide, 197 (52%) received antidepressants; for the men the figure was 291 (33%).

Suicide is associated with CYP450 2D6, 2C19 and 2C9 variants.[39]

Suicide

Many cases of suicide or suicidal ideation are linked with the emergence of ***akathisia*** prior to these events.[29-35]

Non-depressed people i.e. phase I drug trial healthy volunteers,[33, 54] and patients receiving antidepressant treatment for Lyme disease, migraine headaches, insomnia and smoking cessation.[55, 56] have experienced suicidal thoughts.

When non-depressed people become suicidal on antidepressants the mental status changes are inarguably linked with antidepressants.

Homicide/Murder

People committing homicides had genetic variants CYP2D6, CYP2C19 and CYP2 C9.[39]

Avoidance of Suicide Exposure

Various tactics used by the Pharmaceutical Industry to hide the fact their drugs cause iatrogenic suicide: [57]

- Benzodiazepines used for sedation to prevent drug-induced agitation (and *akathisia*) in phase III of the trials.
- Euphemisms such as "emotional lability," "non accidental overdose" and "hostility" are used to minimise and disguise suicidality, completed suicide and homicidality.
- Manipulation of data by "the misattribution of suicidality to placebo when these behaviours occurred during the lead in phase of the trial, or in some cases months after the end of the trial."[9]
- Adverse events during the lead in to trials is claimed to be due to previously administered drug withdrawal effects.

With re-analysis to correct these errors in trial data, SSRIs consistently reveal a higher rate of suicide 2 - 4 times higher than placebo.[58]

Violence

Although there have been no clinical trials involving multiple homicides and genetic screening, data from the Food and Drug Administration Adverse Event Reporting System depict serotonergic antidepressants have been consistently and strongly associated with acts of violence towards others.[59]

This data is supported by an impressive body of research from case reports and population studies for antidepressant associated violence which is available from the International Coalition for Drug Awareness and the Prozac Survivors Support Group website, describing more than 1,600 violent incidents associated with SSRI use in 2009.[60]

In 2010 the number of stories of violence and aggression connected with SSRIs, including murder and murder-suicides was **3,900+.** This number increased to **4,800+** by November 2011.[61]

Violence

Violence may be associated with other behavioural changes such as bizarre quality to thoughts and actions that can be obsessive, compelling and have an unrelenting quality.[19]

Akathisia is a predisposing factor to aggression and violent behaviour[36-39] and the intolerability of ***akathisia*** with the combination of SSRI iatrogenic impaired cognitive functioning causes a reduction in impulse control which can be dangerous.[32]

Prescribers need to be aware behavioural changes are iatrogenic resulting from neurotransmitter disruption and are a genuine and serious ADR.[59]

Although patients who take antidepressants continue to be held responsible for violence and aggression,[43] in view of the above facts accountability needs to be placed with prescribers and the pharmaceutical industry.

Suicide and Violence

Based on the literature and clinical experience, the syndrome of SSRI-induced obsessive suicidality and violence includes many and sometimes all of the following:[19]

- A relatively sudden onset and rapid escalation of the compulsive aggression against self and/or others.
- A recent (typically within two months) initial exposure to the medication, or a recent change in the dose of the medication, or a recent addition or removal of another psychoactive substance to the regimen.
- The presence of other adverse drug reactions often involving ***akathisia*** or stimulation along a continuum from irritability and agitation to agitated depression and mania.

Suicide and Violence cont…

- Resolution of the syndrome after termination of the causative medication, often with a marked overall improvement in the individual's mental status.
- An extremely violent and/or bizarre quality to the thoughts and actions.
- An obsessive, compelling, unrelenting quality to the thoughts and actions.
- An out-of-character quality for the individual as determined by the individual's history.
- An alien or ego-dystonic quality as determined by the individual's subjective report.[19]

Suicide and Violence

Eli Lilly, the maker of SSRI drug Prozac has been aware of Prozac-induced suicidal thoughts and violence since 1984.[62]

Psychologist A. Blake Tracy, Ph.D., author of Prozac: Panacea or Pandora reports that, “The latest figures show Prozac has about 44,000 adverse reports filed with the FDA. Out of those reports there are about 2500 deaths with the large majority of them linked to suicide or violence.[63]

Despite Eli Lilly adamantly denying suicidality and violence as an Adverse Drug Reaction, the company has paid millions of dollars to victims and survivors of Prozac related suicides and murders.[64]

Sleep Behaviour

Transitions from waking to sleeping and Rapid Eye Movement (REM) and non-REM cycles, are controlled by serotonin and acetylcholine mechanisms and occur 4 to 5 times during sleep.[65]

Normal dream sleep occurs during the REM sleep cycle when serotonin activity has fallen to zero and the serotonin neurons in the brainstem are "off" (silent). The inhibitory effect of serotonin on acetylcholine producing cholinergic neurons is removed so these neurons are "on" (firing) which triggers REM-dream sleep.[65]

REM-dreaming activates neurons in the brainstem that inhibit all other motor activity, causing sleep paralysis. In this way the dreamer is prevented from sleepwalking and acting out his/her dreams in real time.[65]

Sleep Behaviour Disorder

REM sleep cycles are disrupted by SSRIs, which results in the repression of dreams and nightmares and the deactivation of 'sleep paralysis'.

Even though a person is seemingly awake, the consequences of SSRI disruption of sleep cycles result in potential 'acting out' of dreams and nightmares in real time, the behavioural status changes being mania and psychosis.[66]

Many individuals report bizarre vivid lifelike dreams whilst on SSRIs. 86% of cases diagnosed with REM sleep behaviour disorder were taking antidepressants.[67] In a state of somnambulism one patient committed homicide.[39]

Psychosis and Mania

There are many research papers depicting patients experiencing mania[68 – 75] and psychosis[8] resulting from 'treatment' with SSRI and SNRI medication.

The short allele of the serotonin transporter gene-linked polymorphic region (5HTTLPR) is associated with mania/psychosis[47, 76] and CYP450 2D6 and 2C19 variants are implicated.[39]

In June 1986 an Eli Lilly proposed draft of "Precaution and Adverse Reactions" sections of the Prozac package insert included; "Mania and psychosis may be precipitated in susceptible patients by antidepressant therapy." This information was not included in the final Patient Information Leaflet.[77]

Psychosis and Mania

Despite **DSM-IV** making reference to antidepressant induced mania: "Symptoms like those seen in a Manic Episode may be due to the direct effects of antidepressant medication ...",[78] neither the commonly sourced UK documents **NICE**,[1] **IAPT**[79] or **Choice & Medication (C&M)**[80] which provides "information about medications used in the mental health setting to help people make informed decisions…", acknowledge SSRI and SNRI medications may cause iatrogenic mania.

This omission serves to foster clinicians' naivety and lack of awareness about antidepressant iatrogenic mania.

Psychosis and Mania

The difficulty lies with the understanding of mania, which ranges in intensity from a mild form to severe that includes psychotic features such as hallucinations.[81] Some professionals who do not understand the full scope of psychotic symptoms associated with mania may mistakenly believe patients are 'unmasking' an underlying condition such as bipolar or schizophrenia.

Early signs and symptoms of SSRI induced psychosis and mania frequently begin with the following mental status changes:

"… lesser degrees of insomnia, nervousness, anxiety, hyperactivity and irritability" and then progress toward more severe agitation, aggression, and varying degrees of mania. Mania or manic-like symptoms include disinhibition, grandiosity, sleep disturbances, and out-of-control aggressive behavior, including cycling into depression and suicidality."[19]

Psychosis and Mania

Psychiatric Hospital Admissions

In a fourteen-month period a survey found 43 (8.1%) of 533 hospital admissions with patients experiencing psychosis or mania were associated with antidepressant medication.[8]

The survey concluded that, '…the rate of admissions due to antidepressant-associated adverse behavioral effects remains significant.'[8]

Mania is a psychotic episode and in a survey, 60% of 400 patients with bipolar disorder reported that their initial diagnosis was depression.[82]

The number of patients per se in the UK who present with the emergence of antidepressant iatrogenic mania and psychosis and who subsequently receive a dual diagnosis or are re - diagnosed as 'schizophrenic' or 'bipolar' is currently unknown. Iatrogenic mania/psychosis needs to be recognised; neuroleptic, i.e. "antipsychotic" prescribing or treatment, inevitably increases drug toxicities and further psychological ADRs.

NICE Guidelines, IAPT and Choice and Medication

NICE Guidelines for Depression[1] and **Choice and Medication,**[80] have conflicting information about antidepressants and suicide.

There is **NO** reference to suicide ideation and completed suicide in association with antidepressants in **Choice and Medication** and **IAPT**,[79] compared with **NICE** Guidelines which does refer to suicide ideation and completed suicide due to antidepressant medications.

DSM-IV

The **DSM-IV** provides consensual evidence for SSRI-induced adverse reactions related to mania, potential aggression and suicide and concedes, "Serotonin-specific reuptake inhibitor [SSRI] antidepressant medications may produce ***akathisia***."[83]

Compromised behavioural functions do need to be taken into account when patients are prescribed serotonergic drugs and potentially there is a way forward to provide evidence to ascertain serotonergic drugs may be responsible for behavioural changes.

Genetic testing for **CYP 450 2D6**[39] metabolising pathways or **SERT** polymorphism would determine patients' genetic susceptibility to SSRI adverse drug reactions. Genetic screening could go a long way to prevent patients from being 'condemned to a lifetime of neuroleptics'[84] and morbidity.

ADRs linked to Antidepressant/Gene Variant Interactions

Akathesia
CYP450 2D6, 2C19 and 2C9.[39] Short allele of the serotonin transporter gene-linked polymorphic region (5HTTLPR)[47]

Suicide
CYP450 2D6, 2C19 and 2C9.[39]

Homicide/Murder
CYP450 2D6, 2C19 and CYP 2C9.[39]

Insomnia
Short allele of the serotonin transporter gene-linked polymorphic region (5HTTLPR).[47]

Mania /Psychosis
The short allele of the serotonin transporter gene-linked polymorphic region (5HTTLPR) [47, 76] is associated with mania/psychosis and CYP450 2D6 and 2C19 variants are implicated.[39]

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Contributors:

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

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