# Targeted Pharmacovigilance for Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitors (SSNRIs)

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## I.    INTRODUCTION

Pharmacovigilance (PV) has been defined by the World Health Organization (WHO) as the science and activities related to the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs).It is one that must be carried out by all those involved in caring for patients on medication, including doctors, nurses, and Pharmacists. The aims of PV arepatient care and safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile ofmedicines. (1)

Indian Pharmacopoeia Commission (IPC) Ghaziabad is functioning as National Coordination Centre (NCC) for Pharmacovigilance Programmed in India (PvPI) to track and monitor all the adverse drug reaction. The Pharmacovigilance Program (PvPI) of India has come a long way since its inception in 2010, an initiative of the Central Drugs Standard Control Organization (CDSCO) under the Ministry of Health and Family Welfare, Government of India. (2)

The World Health Organization defines an Adverse Drug Reaction (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." [WHO Technical Report No 498 (1972)]. This description implies that individual factors may play an important role in drug response, and that the effect is harmful to the patient(3). A "serious adverse reaction means an adverse reaction which is fatal, life-threatening, disabling, incapacitating, or which results in or prolongs hospitalization."

Antidepressants were first developed in the 1950s. Their use has become progressively more common in the last 20 years.In the 1970s, second-generation antidepressants were developed with differing receptor binding activities. They had different side effect profiles, depending on their binding at sites for other classes of receptors (4 &5). The realization that more highly receptor-selective agents would reduce the number and type of adverse effects but with increased "potency" because of their selectivity spurred the development of the class of selective serotonin reuptake inhibitors (SSRIs).

SSRIs are the most commonly prescribed class of antidepressants along with use in treatment anincluding: anxiety, generalized anxiety disorder (GAD), panic disorder, severe phobias, such as agoraphobia and social phobia, bulimia, obsessive compulsive disorder (OCD) and post-traumatic stress disorders (PTSD) and other mood disorders. SSRIs can sometimes be used to treat other conditions, such as premature ejaculation, premenstrual syndrome (PMS), fibromyalgia and irritable bowel syndrome (IBS). Occasionally, they may also be prescribed to treat pain. SSRIs include drugs such as: sertraline (Zoloft), fluoxetine (Prozac, Sarafem), citalopram (Celexa), escitalopram (Lexapro), paroxetine (Paxil, Pexeva, Brisdelle), fluvoxamine (Luvox)(6).

SNRIs help improve serotonin and norepinephrine levels in your brain. The main use of SNRIs is in the treatment of major depression. Other

applications include treatment of pain disorders (including neuropathies and fibromyalgia), generalized anxiety, vasomotor symptoms of menopause and stress urinary incontinence (Susman N, 2003). The class of SNRIs comprises five drus: venlafaxine (Effexor XR, Efexot XR), its metabolite desvenlafaxine (Pristique), milnacipran (Ixel, Toledomin), duloxetine (Cymbalta, Xeristar) and mirtazapine (Remeron) (7).

Both Selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are two classes of antidepressants associated adverse effects such as abnormal thinking, agitation, anxiety, dizziness, headache, insomnia, sexual dysfunction, sedation, tremor, sweating, weight loss, diarrhea, constipation, dry mouth, rash, and nausea. Rarely, SSRIs have been associated with hyponatremia (low sodium), hypoglycemia (low blood glucose), and seizures.

## II.     REVIEW OF LITERATURE

Wilkinson TJ et all studies suggest that post-marketing clinical trials have reported rates of sexual dysfunction as high as 75%. Although severe SSRI-induced hyponatremia was not reported in the original clinical trials, it is now known to occur in 1 in 200 elderly patients per year receiving treatment with fluoxetine or paroxetine [8].

Individually, Goldstein BJ et al in previous studies suggest that postmarketing surveillance studies suggest that fluvoxamine is associated with the highest frequency of GI disturbances, while anxiety, agitation, and insomnia are most often reported with sertraline and fluoxetine. During long-term SSRI therapy, the most troubling adverse effects are sexual dysfunction, weight gain, and sleep disturbance [9].

In February 2018, a review article about PSSD by Coskuner et al raised concerns about the possibilityof long-term sexual consequences for people exposed to SSRIs during pregnancy or at a young age [10].

In May 2018, Healy et al published a study of 300 cases of enduring sexual dysfunction of which 221 were after the previous use of serotonin reuptake inhibitors [11].

Funk KA et al published a study of some SSRI are associated with particular side effects that may not arise as frequently with others, e.g. escitalopram/citalopram and a dose dependent risk of QT interval prolongation. Authors Funk KA et al studies suggest that a recent review of QT interval prolongation potential among the SSRI points to numerous limitation in interpreting available data,

not least that most trials are not designed to examine QT interval changes. However, it concludes that current evidence indicates that QT interval prolongation or the cardiac arrhythmia Torsade de points (Tdp) is reported more frequently with citalopram and escitalopram. Where the other SSRIs are concerned, QT prolongation and Tdp are largely limited to case reports, though there is evidence that paroxetine has the lowest risk for QT prolongation of SSRI [12].

British National Formulary        previous studies suggest that SSRIs have a common mechanism of action and generally, therefore, pharmacodynamics interactions with other drugs are likely to occurs with all SSRIs, e.g. all SSRIs are contraindicated in combination with monoamine oxidase inhibitors (MAOIs) due to risk of serotonin syndrome and there is an increased risk of upper GI bleeding when aspirin is administered with SSRIs [13].

Gartlehner G et al studies suggest that a Meta-analysis of 234 studies of $2^{nd}$ generation antidepressants (including the SSRI and SNRI) conducted on behalf of the agency for Healthcare research and quality in the USA, determined that overall, treatment effects were similar among the SSRIs and SNRIs [14]

*Stewart JW* et al studies suggest that compared with the SSRI class, the SNRI class tends to induce more nausea, insomnia, dry mouth, and in rare cases elevated blood pressure [15].

Voican CS et al recent research supported this early hypothesis, and further showed that among new antidepressants nefazodone, bupropion, duloxetine, and agomelatine have higher risk of liver damage whereas citalopram, escitalopram, paroxetine, and fluvoxamine had lower risks [16].

## III.     AIM& OBJECTIVES

**AIM**
➢        Targeted pharmacovigilance for SSRIs and SSNRIs for psychiatric illness.

**OBJECTIVES**
➢        To identify incidence of adverse drug reaction(s)following use of SSRIs and SNRIs for psychiatric illness.
➢        To conduct retrospective analysis on ADR reported to ADR monitoring centre from January, 2017 till March, 2019 screened for use of SSRI or SNRI.

## IV.    MATERIALS & METHODS

**Study Design**

The study will be hospital-based observational study for capturing and monitoring of all ADR's in patients who receiveSSRIs and SNRIs in Out-patient Department ofPsychiatry at All India Institute of Medical Science, Rishikesh.

Prospective study will be conducted in Out-patient Department of AIIMS, Rishikesh. All patients who receive treatment with SSRIs and SNRIs for psychiatric illness will be interviewed for obtaining information about demographic details, adverse drug reactions, concomitant medications using structured interview. Interview will be conducted after seeking approval from treating physician. No personal questions will be asked during the interview. The information obtained will be kept confidential.

The study will be conducted after obtaining due approval from the Institute Ethics Committee. Patients giving verbal informed consent will be enrolled in the study.

**Study Period**

The study will be carried from January 2017 to March 2019 in the Department of Psychiatry& Department of Pharmacology, AIIMS, Rishikesh.

**Study population**

Patients who will receive targeted drugs (SSRI) and (SNRI) and develop adverse outcome will be enrolled from OPD of Department of Psychiatry AIIMS, Rishikesh.

**Inclusion criteria**

All patients who receive targeted drug therapy (SSRI) and (SNRI) attending Psychiatry O.P.D/IPD at AIIMS, Rishikesh.
1)      Patients from all age groups and both sexes will be included.
2)      Those who will understand the purpose of the study and are ready to provide information regarding their health status.

**Exclusion criteria**

1) Patient not willing to participate;
2) Those unable to comprehend for other reasons.

**Data Collection**

●      Investigator will conduct interview of the patient under supervision of treating physician about Adverse Drug Reactions (ADRs) due to the drugs used in management of patients using a check-list of ADRs (Appendix I).
●      Information pertaining to details regarding patient's demographics, medical history, medical condition, suspected medication and adverse drug reaction will be recorded on Customized Case Record Form (CRF). (Appendix II).
●      If the patient reports any adverse outcome it is to be recorded in Suspected Adverse Drug Reaction Reporting Form of PvPI (Appendix III).

**Data Analysis:**

●      The data will be submitted to ADR Monitoring Centre for further analysis and evaluation.
●      The reported ADR data will be evaluated for establishing causal association between drug and reaction event using WHO UMC Causality Assessment Scale.
●      The study outcome will identifypotential risk factorsfrom the use of SSRI and SNRI in psychiatric illness.
●      The data will analysed statistically and presented graphically using Microsoft Excel

**Data Archival:**

●      The information collected will be kept confidential and data records are maintained electronically and as hard copy files.
●      The data willbe used for scientific purpose only.

**Study tools:**

●      Check list of ADRs (Appendix Ia and I b)
●      Case Record Form (CRF) (Appendix II).
●      Suspected Adverse Drug Reaction Reporting Form (Appendix III)
●      WHO UMC Causality Assessment Scale (Appendix IV)
●      Microsoft Word&Excel

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**APPENDIX I (a)**
**Check list of Adverse Drug Reactions of Antidepressants class of SSRIs**

| ADR | SSRI | | | | | | |
|---|---|---|---|---|---|---|---|
| | Citalopram | Sertraline | Paroxetine | Depoxitine | Escitalopram | Fluvoxamine | Fluoxetine |
| | Y/N | Y/N | Y/N | Y/N | Y/N | Y/N | Y/N |
| Anaphylaxis | | | | | | | |
| Abnormal Bleeding | | | | | | | |
| Bullous Dermatitis | | | | | | | |
| Constipation | | | | | | | |
| Confusion | | | | | | | |
| Cardiac Arrhythmias | | | | | | | |
| Decreased Platelets | | | | | | | |
| Drowsiness/ Sedation | | | | | | | |
| Diarrhea | | | | | | | |
| Dyspepsia | | | | | | | |
| Edema | | | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Glaucoma** | | | | | |
| **Hypoglycemia** | | | | | |
| **Hyperthermia /Heat Stroke** | | | | | |
| **Hallucination/ Psychosis** | | | | | |
| **Hepatitis** | | | | | |
| **Increased Cholesterol** | | | | | |
| **Itching/ Pruritus** | | | | | |
| **Insomnia** | | | | | |
| **Mania** | | | | | |
| **Neuroleptic Malignant Syndrome** | | | | | |
| **Nervousness/ Anxiety** | | | | | |
| **Palpitation** | | | | | |
| **Paralytic Ileus** | | | | | |
| **QT Prolongation** | | | | | |
| **Rash** | | | | | |
| **Serotonin Syndrome** | | | | | |
| **Strokes** | | | | | |
| **Seizures** | | | | | |
| **Sweating** | | | | | |
| **Somnolence** | | | | | |
| **Tremor** | | | | | |
| **Urinary Frequency** | | | | | |
| **Visual Disturbance** | | | | | |
| **Worsening Depression** | | | | | |
| **WBC Changes** | | | | | |
| **Any Other** | | | | | |

**APPENDIX-I (b)**

**Check list of Adverse Drug Reactions of Antidepressants class of SNRIs**

| ADR | SNRI | | | | |
|---|---|---|---|---|---|
| | **Milnacipram** | **Venlafaxine** | **Duloxetine** | **Levomilnacipram** | **Desvenlafaxine** |
| | **Y/N** | **Y/N** | **Y/N** | **Y/N** | **Y/N** |
| **Anaphylaxis** | | | | | |
| **Abnormal Bleeding** | | | | | |
| **Bullous Dermatitis** | | | | | |
| **Constipation** | | | | | |

| | | | | |
|---|---|---|---|---|
| **Confusion** | | | | |
| **Cardiac Arrhythmias** | | | | |
| **Decreased Platelets** | | | | |
| **Drowsiness/ Sedation** | | | | |
| **Diarrhea** | | | | |
| **Dyspepsia** | | | | |
| **Edema** | | | | |
| **Glaucoma** | | | | |
| **Hypoglycemia** | | | | |
| **Hyperthermia /Heat Stroke** | | | | |
| **Hallucination/ Psychosis** | | | | |
| **Hepatitis** | | | | |
| **Increased Cholesterol** | | | | |
| **Itching/ Pruritus** | | | | |
| **Insomnia** | | | | |
| **Mania** | | | | |
| **Neuroleptic Malignant Syndrome** | | | | |
| **Nervousness/ Anxiety** | | | | |
| **Palpitation** | | | | |
| **Paralytic Ileus** | | | | |
| **QT Prolongation** | | | | |
| **Rash** | | | | |
| **Serotonin Syndrome** | | | | |
| **Strokes** | | | | |
| **Seizures** | | | | |
| **Sweating** | | | | |
| **Somnolence** | | | | |
| **Tremor** | | | | |
| **Urinary Frequency** | | | | |
| **Visual Disturbance** | | | | |
| **Worsening Depression** | | | | |
| **WBC Changes** | | | | |

| Any Other | | | | | |
|---|---|---|---|---|---|

**APPENDIX-IICASE RECORD FORM**

| CR NO.: - | | | TELEPHONE/ADDRESS:- | | |
|---|---|---|---|---|---|
| UHID:- | | | | | |
| PATIENT INITIALS | AGE (YEARS) | | WEIGHT (kg)/HEIGHT (cm) | | GENDER (M/F) |
| RELEVANT TEST: | | | MEDICAL HISTORY: | | |
| EACTION/PROBLEM:- | | | INDICATION:- | | |
| **SUSPECTED MEDICATION**:- | | | | | |
| DRUG NAME | DOSE USED | ROUTE USED | FREQUENCY | THERAPY STARTED | THERAPY STOPPED |
| 1. | | | | | |
| 2. | | | | | |
| **CONCOMITANT MEDICATION**:- | | | | | |
| DRUG NAME | DOSE USED | ROUTE USED | FREQUENCY | THERAPY STARTED | THERAPY STOPPED |
| 1. | | | | | |
| 2. | | | | | |
| 3. | | | | | |
| DATE OF REACTION STARTED:- | | | OUTCOMES:- | | |
| DATE OF RECOVERY:- | | | SERIOUSNESS:- | | |
| ACTION TAKEN:- | | | | | |
| **INDICATION: -** | | | | | |
| SUSPECTED DRUG | | | CONCOMITANT DRUG | | |
| 1. | | | 1. | | |
| 2. | | | 2. | | |
| 3. | | | 3. | | |

**APPENDIX-III ADR FORM**

## SUSPECTED ADVERSE DRUG REACTION REPORTING FORM
For VOLUNTARY reporting of Adverse Drug Reaction by Healthcare Professionals
**INDIAN PHARMACOPOEIA COMMISSION**(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India Sector-23, Raj Nagar, Ghaziabad-201002

| A. PATIENT INFORMATION | | | |
|---|---|---|---|
| 1. Patient Initials _____ _____ | 2. Age at the time of Event or Date of Birth _____ _____ | 3. M ☐    F ☐    Other ☐ | Reg. No. /IPD No. /OPD No. /CR No. : |
| | | 4. Weight_____Kgs | AMC Report No.        : |
| | | | Worldwide Unique No. : |

**B. SUSPECTED ADVERSE REACTION**

5. Event/Reaction start date (dd/mm/yyyy)
6. Event/Reaction stop date (dd/mm/yyyy)
6 (A). Onset Lag Time
7. Describe Event/Reaction with treatment details, if any

12. Relevant tests/ laboratory data with dates

13. Relevant medical/medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction, past surgery etc.)

14. Seriousness of the reaction: No ☐ if Yes ☐(please tick anyone)
☐ Death (dd/mm/yyyy)        ☐ Congenital-anomaly
☐ Life threatening        ☐ Disability
☐Hospitalization/Prolonged        ☐ Other Medically important

15. Outcomes
☐ Recovered    ☐ Recovering    ☐ Not recovered
☐ Fatal    ☐ Recovered with sequelae ☐ Unknown

**C. SUSPECTED MEDICATION(S)**

| S.No | 8. Name (Brand/Generic) | Manufacturer (if known) | Batch No. / Lot No. | Exp. Date (if known) | Dose used | Route used | Frequency (OD, BD etc.) | Therapy dates — Date started | Therapy dates — Date stopped | Indication | Causality Assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| i | | | | | | | | | | | |
| ii | | | | | | | | | | | |
| iii | | | | | | | | | | | |
| iv* | | | | | | | | | | | |

| S.No as per C | 9. Action Taken (please tick) — Drug withdrawn | Dose increased | Dose reduced | Dose not changed | Not applicable | Unknown | 10. Reaction reappeared after reintroduction (please tick) — Yes | No | Effect unknown | Dose (if reintroduced) |
|---|---|---|---|---|---|---|---|---|---|---|
| i | | | | | | | | | | |
| ii | | | | | | | | | | |
| iii | | | | | | | | | | |
| iv | | | | | | | | | | |

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

| S.No | Name (Brand/Generic) | Dose used | Route used | Frequency (OD, BD, etc.) | Therapy dates — Date started | Therapy dates — Date stopped | Indication |
|---|---|---|---|---|---|---|---|
| i | | | | | | | |
| ii | | | | | | | |
| iii* | | | | | | | |

Additional Information:

**D. REPORTER DETAILS**

16. Name and Professional Address:_____
_____
Pin:_____E-mail_____
Tel. No. (with STD code)_____
Occupation:_____ Signature:_____

17. Date of this report (dd/mm/yyyy):

**Sig. and Name of Receiver-**

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction. Submission of an ADR report does not have any legal implication on the reporter.

**APPENDIX IV:WHO UMC CAUSALITY ASSESSMENT SCALE**

| CAUSALITY TERM | ASSESSMENT CRITERIA |
|---|---|
| **Certain** | • Event or laboratory test abnormality, with plausible time relationship to drug intake<br>• Cannot be explained disease or other drugs<br>• Response to withdrawal plausible (pharmacologically, pathologically)<br>• Event definitive pharmacologically phenomenologically (example an objective and specific medical disorder or recognized pharmacological phenomenon<br>• Rechallenge satisfactory , if necessary |
| **Probable/ Likely** | • Event orlaboratory test abnormality, with reasonable time relationship to drug intake<br>• Unlikely to be attributed to disease or other drugs<br>• Response to withdrawal clinically reasonable<br>• Rechallenge not required |
| **Possible** | • Event orlaboratory test abnormality, with reasonable time relationship to drug intake<br>• Could also be explained by disease or other drugs<br>• Information on drug withdrawal may be lacking or unclear |
| **Unlikely** | • Event orlaboratory test abnormality, with a time to drug intake that make a relationship improbable (but not impossible)<br>• Disease or other drug provide  plausible explanations |
| **Conditional / Unclassified** | • Event orlaboratory test abnormality<br>• More data for proper assessment needed or<br>• Additional data under examination |
| **Unassessable/ Unclassified** | • Report suggesting an adverse reaction<br>• Cannot be judged because information is insufficient orcontradictory<br>• Data cannot be supplemented or verified |