Risks of antidepressant induced psychotic events in patients with depression and psychosis

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Abstract

The aim of this 'literature review'-based argumentative paper has been to find out the risks of developing psychotic and depressive disorders in patients having been treated with antidepressants. In order to reach a resounding supposition, this literature review-based argumentative study had taken an incisive look into previous research works and meta-analysis, which in effect had underscored the risks of antidepressant-induced psychotic and depressive disorders in patients with depression as well as psychosis even as the protagonists of antidepressant drug classes could not be undermined given their upscaled magnitude of benefits. While following a probing interpretation of past studies, this might be demystified that antidepressants could lead to psychotic events and depressive disorders in patients of all age groups with children and young adults being more susceptible to develop psychosis. The psychotic episodes could even be developed during initial phase of treatments in patients suffering from depressive and psychotic disorders such as bipolar mood disorder, unipolar depression, major depressive disorders, mania, OCD (Obsessive Compulsive Disorder), delusional depression (psychotic depression), schizophrenia, schizoaffective disorders alongside multiple somatic symptoms among others as well. Concomitantly, with efficaciousness of antidepressants in major depressive disorder still remaining a subject to utter dubitability, different antidepressant drug classes were found to be associated with a considerable scale of adverse effects after carrying out protracted arguments on findings of evidence-based past studies, meta-analysis of previous researches and relevant clinical cases. Therefore, following a systematized approach towards past studies, this argumentative research has reached a coherent conclusion that anti-depressants are likely to cause psychotic events and exaggeration of depressive disorders up to some extent in several cases. Hence, there is a stipulation of individual risk-benefit assessment and intricate history taking in patients being contemplated for antidepressant drugs alongside a close observation and follow-up in patients of all age groups after introducing antidepressant medications.

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1.0. Introduction

1.1. Preface

Antidepressant has been one of the most prescribed medications in adults, children and adolescents along with elderly patients despite a number of antidepressant drug classes' relative lack of benefits in treatment of psychotic events and depressive disorders, in particular major depressive disorder, alongside their adverse effects. However, it remains a crucial challenge to precisely identify whether antidepressants' beneficial effects could outweigh the risks of adverse effects involving psychotic episodes and depressive disorders as stated by Kirsch et al., and Fournier et al., back in the 2008s and 2010s respectively [Kirsch et al., 2008; Fournier et al., 2010]. Evidence-based previous research works had led to an assumptive countersignature that antidepressants, in particular SSRIs (Selective Serotonin Reuptake Inhibitor), have frequently been associated with wide-ranging aberrations in behavioural and metal state in a patient with nascent risk factors, as potential adverse effects could include a deluge of disorders such as agitation, agitated depression, obsessive perceptions or OCDs (Obsessive Compulsive Disorders), manic psychosis, personality disorders alongside akathisia among others. Life threatening Serotonin Syndrome has been frequently related to use of atypical antidepressants with serotonergic functions. Evidences of SSRI-induced deterioration in metal states such as an increase in suicidal ideation, violence and exacerbation of extreme manic phases could be founded in clinical reports, controlled trials along with studies on children and adolescences, according to Broaden et al., (2020) [Broaden et al., 2020]. Despite having a decisive role in treatment of depressive disorders, TCAs (Tricyclic antidepressants), in tandem, had often been found to be less efficacious with potentials to wielding several side effects including anticholinergic delirium alongside delusional depression, suggested Karlsson, I., in 1999 [Karlsson, I., 1999]. In according to quite a lot of clinical studies, use of antidepressants in child and adolescents with anxiety disorders, depressions and obsessive compulsive disorders (OCD), have been linked with adverse effects like of suicidal ideation, psychosis and mania among others, suggested Strawn et al., (2015) along with Safer and Zito (2006) [Strawn et al., 2015; Safer and Zito, 2006]. Practice of antidepressant medications

in pregnancies could be very common, though physicians prescribing antidepressants to pregnant women with depression ought to consider potential foetal risks, in particular in exercise of SSRIs or SNRIs (Serotonin Norepinephrine Reuptake inhibitors). Gao et al., as well as Koren and Nordeng had addressed in 2018 and 2012, respectively [Gao et al., 2018; Koren and Nordeng, 2012].

Concomitantly, although, several antidepressant drug classes are often prescribed in treating depression, anxiety disorders, OCDs and PTSD (Post Traumatic Stress Disorder), up to a two-third of the patients with major depressive disorder had not appositely responded during administration of their first antidepressant drug class as illustrated by Little, A., (2009) [Little, A., 2009]. According to Jonas and Pope (1984) as well as Pope et al., (1985), patients having treated with SSRIs or SNRIs (Serotonin Norepinephrine Reuptake Inhibitor) might elicit symptoms of personality disorder or borderline personality disorder traits [Jonas and Pope, 1984; Pope et al., 1985]. Furthermore, a deluge of evidences, which have been discussed later in this study, found that patients having been treated with antidepressants had required hospital admission because of psychotic episodes, exacerbation of mood disorders, violence, suicidal tendencies, personality disorders, depressive illness and psychotic depression among others. Although, while treating adult patients with multiple somatic symptoms, antidepressants have been found to be highly efficacious, yet adverse effects of some antidepressant drug classes could intensify somatic symptoms, suggested Kleinstäuber, M., (2014) [Kleinstäuber, M., 2014]. According to Hill, Coupland and Morriss (2015), risks of developing status epilepticus are significantly higher in all classes of antidepressants aside from psychosis and depressive disorders [Hill, Coupland and Morriss, 2015].

Nevertheless, gazing at the flipside, Gartlehner et al., suggested in 2019 that several past research works had exposed a higher efficacy of newer generation antidepressants in order to treat depressions regardless of their extent of severity, while newer antidepressants had been found to be more effective in treating patients suffering from seasonal affective disorders or recurrent major depressive disorders [Gartlehner et al., 2019]. Likewise, according to a practice guideline from APA (American Psychiatric Association) released back in 2010s, newer generation antidepressants have been comparatively beneficial to treat

initial symptoms of major depressive disorders [APA, 2010], while Qaseem, Snow and Denberg had accentuated in 2008 that newer generation Antidepressants are found to be widely used as a first line of treatment in patients with major depressive disorders considering their safety profile and risk-benefit ratio in comparison to TCAs [Qaseem, Snow and Denberg, 2008]. According to Amsterdam, J., D., (2006) and Zisook, S., (1985), despite having had an infrequent use as an antidepressant, past researches had revealed that MAOIs (Mono Amine Oxidase Inhibitors) could be a potential therapeutic agent in patients suffering from SSRI-resistant major depression, panic disorder as well as other anxiety disorders, who had not responded well at their first line of treatment [Amsterdam, J., D., 2006; Zisook, S., 1985]. Nonetheless, Tollefson, G., D., had addressed in 1985 that contemplating MAOIs' extensive drug interactions which could come up with intense risks of developing life-threatening side-effects in case of not being monitored properly such as Tyramine Reaction, Serotonin Syndrome as well as an increase in sympathomimetic activity, precise observation and follow-up ought to be recommended in patients being treated with MAOIs or having considered for MAOIs, [Tollefson, G., D., 1985].

1.2. History of anti-depressants and its relation to psychosis since inception

1.2.1. Origin of antidepressants

Antidepressants' journey had been instigated with opioid analgesics alongside methamphetamine. Both of them had been practiced before 1950s as antidepressants, but, were discontinued later due to their addictive properties, according to Weber and Emrich (1988) and Heal et al., (June 2013) [Weber and Emrich, 1988; Heal et al., 2013].

According to Healy, D., (1996), back in the 1951s, Irving Sellikoff and Edward H. Robitzek had begun a clinical trial on two newer anti-tubercular drugs such as Isoniazid and Iproniazid and the drugs had responded quite dramatically [Healy, D., 1996]. A year later, Max Lurie and Harry Salzer had discovered their antidepressant properties, which the anti-tubercular drugs had been found to be exerting as a weak

inhibitor of MAO-A (mono amine oxidase A). López-Muñoz et al., (2007) had mentioned in a journal of clinical psychopharmacology that Iproniazid had been discontinued later in 1961 following reports of its potentially lethal hepatotoxicity, [López-Muñoz et al., 2007].

According to Kuhn, R., (1958), among a barrage of research works on antidepressants which had been conducted in the 1950s, Ronald Kuhn had developed the world's first tricyclic with an antidepressant property in 1957. Nevertheless, chlorpromazine, often known as the "Laborit's Drug," as Laborit had trialled the drug since 1952 in a military hospital in France as an anaesthetic booster with a pre-operative dose between 50mg to 100mg and found to be effectual in inducing an artificial hibernation, was released into the market in 1953 as a medication to treat mania, schizophrenia, psychosis alongside psychomotor excitement and led to the discovery of antidepressants as well [Kuhn, R., 1958].

1.2.2. Relation of anti-depressant with psychosis since orientation

Several antidepressants could lead to psychotic events ranging from major depressive disorder to psychosis and mania as beforementioned. Surprisingly, since the beginning of introduction of antidepressants to treat bipolar disorders, a number of research works had been published revealing antidepressant-induced mania. In terms of TCA antidepressants, Wehr and Goodwin (1987) had established that TCAs (Tricyclic Antidepressants) could lead to hypomania or mania with a worsening of bipolar disorder by accelerating the disorder's cycle frequency (Wehr and Goodwin, 1987). Harmoniously, Goldberg and Truman had addressed in 2003 that about 25 per cent to 30 per cent patients with bipolar disorder could be highly susceptible to antidepressant-induced mania. Adding further holocaust, irrespective of the antidepressants' drug classes, about 20 per cent to 40 per cent bipolar disorder patients being treated with antidepressants, could develop mania or hypomania. Moreover, antidepressants' clinical efficacy in treating the depressive stage of bipolar disorder, remained subject to further qualms. Besides, multiple research works had reached a smilar finding that a treatment approach with TCA could increase the risk of antidepressant-induced mania or hypomania than that of non-TCA medications in unipolar depression [Goldman and Truman, 2003]. Furthermore, El-Fakahany and

Richelson (1983) had underscored that patients being treated with TCAs had experienced a much-higher risk of manic switch than those with other antidepressant drug classes [El-Fakahany and Richelson, 1985].

When it comes to SSRI, soon after the marketing of first SSRI, fluoxetine, in the US back in the January of 1988, a flurry of reports began to emerge depicting fluoxetine-induced injury to self and others. Two years later, the US FDA had ordered the manufacturers to label the drug with risks of plausible "suicidal ideation" alongside "violent behaviour." An APA (American Psychiatric Association) practice guideline published in 1993 had unveiled (APA, 1993)." Another SSRI, Paroxetine, had received US FDA (Food and Drug Administration) warning in 2003 following reports of its role to surge the risks of inflicting harm to self and others as well as suicidal behaviour in children and teens under the age of 18 [Food and Drug Administration, 2003]. According to Wyeth Pharmaceuticals, Venlafaxine, an SNRI (Serotonin Norepinephrine Reuptake Inhibitor), had received a smilar warnng in the 23rd of August, 2003 [Wyeth Pharmaceuticals, 2003, August the 23rd)]. Aside from that, Coupland et al., had found in separate studies in 2011 and 2015 that Mirtazapine, a tetracyclic antidepressant (TeCA) used mostly as a mood stabilizer, had shown an increased suicidal risk [Coupland et at., 2011; Coupland et al., 2015]. In tandem, all classes of antidepressant might increase the risks of epilepsy and seizure as beforementioned [Hill, Coupland and Morris, 2015].

2.0. Literature review

Being a literature review-based argumentative research, past studies addressing the risks of antidepressant-induced psychotic events in patients with depressive disorders and psychosis have been dissected in this section with an exhaustive approach. This particular section would also confer case studies related to anti-depressant induced psychotic events requiring hospital admissions as well as withdrawal effects of antidepressant drugs. However, this review of past literatures and meta-analysis of case studies would underscore risks as well as benefits of using newer generation antidepressants which could reduce the chances of developing potential adverse effects and drug interactions. Besides, considering an upscaled efficacy of use of MAOIs in patients with major depressive disorder who are tolerant to other antidepressant drug classes despite their widespread drug interaction, a review of past research works regarding benefits of using MAOIs in patients suffering from major depressive disorder had been conducted.

In order to reach a comparatively vindicative conclusion, different antidepressant drug classes along with their benefits as well as risks have been discussed from wide-ranging crow's nests.

2.1. Depression and anti-depressants

Depression could be referred to a psychoneurotic disorder characterized by lack of interest, lack of appetite, loss of libido, lack of concentration, feeling of dejection and unjustified self-guilt, altered sleeping pattern alongside development of suicidal ideations, Rakel, R., had defined back in 1999s [Rakel, R., 1999].

As depression has been a recurrent and common disorder that might cause a significant scale of morbidity and mortality across the globe, a proper, precise and relevant use of anti-depressant is widely anticipated, though, Bech, P., (2010) had unveiled that older generation or conventional antidepressants such as TCAs had often been associated with higher complaints of inefficacy alongside adverse effects. [Bech, P., 2010].

Inclusively, typical antidepressant compounds could be defined as agents that could inhibit monoamine oxidase, hence increasing concentration of monoamine neurotransmitters such as serotonin, dopamine and norepinephrine in synaptic clefts, as monoamine oxidase catalyses the breakdown of monoamine neurotransmitters. Despite a higher success rate of typical antidepressants in mild and moderate depressive disorders, they have limitations such as a delayed onset along with association of higher adverse effects as it has been stated in '*Goodman & Gilman's the Pharmacological Basis of Therapeutics'* (2017) ['*Goodman & Gilman's the Pharmacological Basis of Therapeutics*,' 2017].

In general, antidepressants could be informally classified into five major sub-groups which are listed below as it had been stated by Khushboo and Sharma (2017).

- TCAs (Amitriptyline)
- SSRIs (Fluoxetine, Paroxetine)
- MAOIs (Phenelzine, Selegiline, Moclobemide)
- SNRIs (Venlafaxine)
- Newer generation non-TCA antidepressants (Mirtazapine, Agomelatine)

[Khushboo and Sharma, 2017]

2.2. Classifying antidepressants

Nevertheless, according to mechanism of action, antidepressants could be classified into following groups in a more germane manner, as Alvano and Zieher had illustrated in 2019.

Class A: Monoamine modulators

- Class A I: MAOIs
    1. A1a: Irreversible non-selective MAOIs (Isocarboxazid, Phenelzine, Tranylcypromine)
    2. A1b: Irreversible selective MAOIs: Selective MAO-B Inhibitors (Selegiline)
    3. A1C: Reversible selective MAOIs: Selective MAO-A Inhibitors (Moclobemide)
- Class A II: Neuronal reuptake inhibitors

1. AIIa: Relatively selective serotonergic (Selective Serotonin Reuptake Inhibitors (SSRIs)- Fluoxetine, Sertraline, Paroxetine, Escitalopram, Citalopram, Fluvoxamine)
2. AIIb: Serotonin non-epinephrine reuptake inhibitor (SNRIs) (Serotonergic & noradrenergic- Venlafaxine, Desvenlafaxine, Duloxetine, Levomilanacipran)
3. AIIc: Norepinephrine Dopamine reuptake inhibitor (NDRI) (Noradrenergic & Dopaminergic- Bupropion)

- Class AIII: Noradrenergic and specific serotonergic antidepressants (NaSSa) (Alpha-2 receptor antagonists- Mirtazapine)
- Class AIV: Multimodal

1. AIVa: Serotonergic (Vortioxetine, Trazodone, Vilazodone)
2. AIVb: Noradrenergic (Maprotiline, Manserine)
3. AIVc: Noradrenergic and Serotonergic with muscarinic antagonism (Imipramine, Clorimipramine, Desipramine, Amitriptyline, Nortriptyline)

Class B: non-Monoaminergic modulators

- Melatonin receptors agonists (MT1 and MT2) Agomelatine

Class C: Drugs in developmental phase

[Alvano and Zieher, 2019]

However, a review of a study of SmithKline Beecham conducted by Le Noury, Nardo and Healy (2015) that involved a comparison of efficacy of paroxetine and imipramine alongside placebo in adolescents with unipolar major depression, had unveiled that neither paroxetine nor imipramine had shown efficacy in treating major depressions, while there had been higher risks of harms in both drugs [Le Noury, Nardo and Healy, 2015].

Nonetheless, an impact of bias on developing psychotic events and inefficacy in treatment of Antidepressant remained a major limitation, as authors of anti-depressants studies have been receiving

renewed criticisms over recent past, while Turner et al., (2008) had claimed to have found a potential indication of concealing evidences regarding efficacy of antidepressants while comparing clinical trials of 74 US FDA-registered antidepressant drugs [Turner et al., 2008].

Furthermore, many pragmatic problems are emerging in interpretation of antidepressants' efficacies in treating mild, moderate and major depressive disorders. However, Gibson, Hur and Brown (2012) had recently probed and found short-term efficacies of antidepressants in treating depressive disorders in youth, adults and elderly [Gibson, Hur and Brown, 2012].

2.3. Risk of developing psychosis in anti-depressant therapy

When it comes to antidepressant treatments, concerns on plausible side effects and adverse reactions including psychotic events and depressive disorders have continued to impact public perception of antidepressant agents. Even though, antidepressant drug classes are often found to be effective in mild and moderate symptoms, nonetheless, efficacy of antidepressants in major depressive disorders are frequently questioned as beforementioned.

In a diagnostic standpoint, psychotic disorders are the following as stated by Cardinal and Bullmore in 2011.

- Schizophrenia and schizophreniform disorders: Auditory hallucination, broadcasting of thoughts, delusions, disorganized thoughts or cognitive impairment
- Affective (mood) disorders: Major Depression, bipolar disorders and unipolar disorder
- Schizoaffective disorder: Abnormal thought process with unstable mood
- Acute psychotic disorders: often accompanied by emotional turmoil lasting between 1 day to 1 month
- Persistent delusional disorder: usually accompanies hallucinations, mood disorders
- Chronic hallucinatory psychosis: a mental and behavioural disorder

Besides, psychotic symptoms could also involve the followings.

- Personality disorder
- Certain personality disorders (Paranoid, Schizoid or borderline personality disorder)
- Major depressive disorder with or without presence of psychotic incidences
- Bipolar disorder including manic phase or mixed episodes
- PTSD (Post traumatic stress disorder)
- OCD (Obsessive Compulsive Disorder)
- Dissociative Disorder (often associated with breakdown of memory, awareness, identity and perception of realty

However, fewer psychotic incidences could take place in menstruation, postpartum period and in use of stimulant drugs among others, while those psychotic events could be the following.

- Menstrual Psychosis,
- Postpartum Psychosis
- Myxedematous psychosis (dementia in patients with Hashimoto's Thyroiditis)
- Monothematic delusions (multi- or poly-thematic delusions)
- Stimulant psychosis
- Shared psychosis (a delusional thought or belief that spread from one person to another in a particular community)
- Tardive psychosis (often associated with long-term use of neuroleptics).

[Cardinal and Bullmore, 2011]

2.3.1. Psychosis, depression and mood switch in Bipolar Disorders following TCA and non-TCA antidepressants medication

In terms of risks of developing psychosis with antidepressant treatment in a patient with bipolar disorder, incidences of mania or hypomania are very common. Though, Chun and Dunner (2004) highlighted that it still remained uncertain whether antidepressants could trigger the expression of an underlying bipolar

disorder [Chun and Dunner, 2004]. However, according to Gijsman, Geddes and Rendell (2004), acute mania had been reported in patients who had been treated with TCAs alongside SNRIs such as Venlafaxine. [Gijsman, Geddes and Rendell, 2004]

Moreover, Luciano, Sposato and Osvaldo (2014) had found that the antidepressants, which could be used as an antiparkinsonian agent such as MAO-B inhibitor (Selegiline), had shown an increased risk of developing visual and auditory hallucination [Luciano, Sposato and Osvaldo, 2014]. The symptoms could also be associated with false beliefs (delusional thoughts) or false perception of realty. Patients with Parkinson's Disease having been treated with antiparkinsonian antidepressants (MAO-B inhibitor) were found to be in greater risk of developing psychosis than those who were even not being treated, suggested Goetz, C., (2008) [Goetz, C., 2008].

Furthermore, previous studies had reported a higher risk of switch to manic phase or acute psychosis in bipolar patients who had been treated with antidepressants for their depressive episodes. A previous study reviewed by Goldman and Truman (2003) aimed at revealing the risks of antidepressant-induced mood conversion in patients with Bipolar Disorder, had unfurled that about 33 per cent patients had developed AD induced mood conversion, while 36 per cent patients being treated with TCA Antidepressant had developed mood switch and about 17 per cent patients being treated with non-TCA Antidepressant had been met with a switch to mania [Goldman and Trumann, 2003].

Besides, a higher incidence of antidepressant-induced mood conversion in patients with bipolar disorder had been reported in numerous previous research studies based on clinical records. In particular, Goldman and Truman had reported that about a quarter of Bipolar Disorder patients are highly prone to developing antidepressants induced mania [Goldman and Trumann, 2003], while Ghamei et al., (2003) had found out that a manic or psychotic switch in Bipolar Disorder patients being treated with antidepressants, would highly likely to take place during initial phase of treatment, when the depressive disorders had not even been severe [Ghaemi et al., 2003]. Furthermore, Peet, M., (1994) had found out in a retrospective study that the ratio of TCA and non-TCA antidepressants induced psychosis in Bipolar Disorder patients, could

be 12 per cent to 6 per cent [Peet, M., 1994]. Although, the pharmacological mechanism of antidepressant-induced psychosis and mania in Bipolar Disorder patients had been poorly understood, a study conducted by Bunney, W., E., (1978) had found out that a catecholaminergic mechanism in lieu of serotonergic effects could be related to manic switch [Bunney, W., E., 1978]. According to a study conducted by El-Fakahany and Richelson (1983), Amitriptyline, Imipramine and Clomipramine had shown a frequency rate of 42 per cent, 40 per cent and 35 per cent, respectively, in antidepressant-induced switch to mania or psychosis in patients with Bipolar Disorder, while Doxepin, Desipiramin, Mianserin and Trazodone had shown a frequency rate of 26 per cent, 18 per cent, 10 per cent and 9 per cent respectively [El-Fakahany and Richelson, 1983].

Moreover, Coupland et al., (2018) had found out in a cohort control study which included 238,963 patients aged between 20-64 years with depression that SSRIs had a higher rate of adverse effects and mortality than those who had been treated with TCA Antidepressant [Coupland et al., 2018].

Nonetheless, Stahl and Muntner (2013) had found that TCA antidepressants had shown a higher risk of developing anticholinergic delirium in patients with depression, as TCA antidepressants prevent norepinephrine and serotonin reuptake apart from blocking muscarinic receptor, eventually leading to anticholinergic delirium [Stahl and Muntner, 2013]. Blocking of peripheral M1 receptors alongside other muscarinic receptors like of M2, M3, M4 could lead to additional anticholinergic symptoms such as dry mount, blurred vision, constipation and urinary retention among others as suggested by Karlsson, I., (1999) [Karlsson, I., 1999]. Due to having a role in blocking central antimuscarinic activity, TCA antidepressant induces anticholinergic delirium could have been contemplated as a potential complication.

Alongside this, in what could be viewed as a vivid vindication of an exacerbation of psychotic events or depressive disorder in treating patients with unipolar major depression using TCA antidepressants, Glassmen, Kantor and Shostak (1975) had found an exacerbation in delusional depression, a subtype of unipolar depression, in use of TCA antidepressant [Glassmen, Kantor and Shostak, 1975], while Nelson

et al., (1984) had addressed that TCA antidepressants could have had poor response in treating patients with unipolar depression [Nelson et al., 1984].

2.3.2. Complications of antidepressant in patients with schizophrenia

About 25 per cent patients with Schizophrenia might develop depressions and require antidepressant treatment. A meta-analysis of previous research works conducted by Lako et al., had found in 2012 [Lako et al., 2012]. Besides, Siris and Bench (2003) had addressed that past cross-sectional research works also had found a profound relationship between schizophrenia and depressive symptoms as well as more severe psychopathology [Siris and Bench, 2003]. Furthermore, Baynes et al. (2000) had found out that depressive symptoms in patients with schizophrenia had not been associated with age, sex and duration of illness [Baynes et al., 2000] and depressive symptoms might be present in all phases of schizophrenia, however the highest prevalence had been found in patients during acute psychotic episodes, according to Koreen et al., (1993) [Koreen et al., (1993)]. Angermeyer, Kuhn and Goldstein (1990) had underscored that newer antidepressants such as Aripiprazole, Venlafaxine and Mirtazapine among others had been found to be frequently prescribed in clinical practices to treat Schizophrenia or Schizophrenia-related depressive disorders, while a combination of atypical antipsychotic drugs such as Clozapine and Olanzapine with antidepressants like of Venlafaxine as well as Mirtazapine had been found to be highly efficacious. Besides, newer antidepressants could be effective as a prophylaxis to treat associated anxiety or recurrent of events as well [Angermeyer, Kuhn and Goldstein, 1990].

Nonetheless, gazing at the flipside, Plasky, P. (1991) had highlighted that combining antidepressants with antipsychotics to treat Schizophrenia might lead to an increase in risks of adverse effects and drug interactions, while TCA-induced anti-cholinergic symptoms, which might have turned out to be potentially life-threatening in some cases, had been observed in schizophrenic patients. Moreover, patients suffering over more than one year had been found to be more susceptible to developing severe psychopathology what in effect would increase the risks of developing depressive symptoms, thereby leading to an increase in use of an Antidepressant-antipsychotic combination therapy [Plasky, P., 1991].

Still, when it comes to Schizophrenia and Schizoaffective Disorders, benefits of newer generation antidepressants largely outweigh the risks.

2.3.3. Suicidality, violence and mania in SSRI

Even after being one of the most prescribed antidepressants across the globe, while making observations in clinical practices as well as scientific literature reviews unveiling bothersome effects of SSRIs, often these drugs have been treated as a single class of pharmacological agents which could induce adverse mental and behavioural effects like of mania or agitation. Adding further holocaust, if a psychotic disorder has been observed in a case linked to a particular SSRI, similar manic phases would highly likely to be experienced with other SSRIs, suggested APA (American Psychiatric Association) in 1994 in the fourth edition of DSM-IV [Please see Appendix E] [APA, 1994].

2.3.3.1. SSRI induced mania and psychosis

As it has been mentioned earlier that all classes of US FDA-approved SSRIs had been found to be closely related to mania and, Preda et al., (2001) had found out in a retrospective study including 533 psychiatric hospital admissions over a period of fourteen months that about an 8.1 per cent patients had been suffering from antidepressant-induced mania or psychosis, in particular SSRIs, while SSRIs had led to a roughly 70 per cent of all disorders. Atypical Antidepressant such as venlafaxine, nefazodone along with buproprion had resulted 21 per cent of psychotic disorders. TCA antidepressants also had caused nearly a 21 per cent of all psychotic or manic episodes. The total percentage points had exceeded 100 per cent as there had been overlapping in medications.

In what could be contemplated as a more disturbing evidence, more than a third of the hospital admissions had been linked to new onset of mania or psychosis. Among those cases, over a 5 per cent patients had developed extremely severe psychosis or manias with a 42-year-old woman admitting with a history of one-year long depression had begun to experience perception of new location and commanded her in auditory hallucinations to kill herself. A 52-year-old woman had developed an identical disorder and a 49-year-old woman having treated with venlafaxine for mood disorders had developed severe

paranoia. All of them had shown radical improvement after discontinuation of antidepressant medication [Preda et al.,2001].

2.3.4. Serotonin syndrome

Serotonin Syndrome is a potentially life-threatening situation which could be resulted from induction of antidepressants having had serotonergic activity, while serotonin syndrome could occur even during Antidepressant switching and withdrawal.

According to Buckley, Dawson and Isbister (2014), Serotonergic Antidepressant such as agomelatine, fluvoxamine alongside Vortioxetines (a selective serotonin reuptake inhibitor that has possible serotonergic effects) could interact with a number of drugs acting on CNS and PNS and might lead to Serotonin Syndrome, severe symptoms of which usually include agitation, convulsion, delirium, diaphoresis, diarrhoea, mydriasis, myoclonus, muscular rigidity, tachycardia, hyperthermia and hypertension among others.

Due to having a longer half-life, switching from SSRIs such as Fluoxetine could result in Serotonin Syndromes, if clomipramine, fluvoxamine or MAOIs are introduced before a precise and adequate removal of fluoxetine from blood stream. Besides, switching from irreversible MAOIs such as Phenelzine require a close monitoring and precise removal from blood stream before another serotonergic antidepressant could be added to limit the risks of Serotonin Syndrome. [Buckley, Dawson and Isbister, 2014]

Furthermore, according to Gillman, P., K., (2007) a combination of MAOIs with 5-HT blockers such as chlorpheniramine could cause to Serotonin Syndrome. [Gillman, P., K., 2007]

2.3.5. Risks of MAOIs with comparative benefits

Monoamine oxidase neurotransmitter reuptake inhibitors are not widely prescribed given their extent of drug interactions despite exerting potential antidepressant action as Amsterdam, J., D., had stated back in 2006s [Amsterdam, J., D., 2006].

Besides, MAOIs should not be contemplated as a first-line treatment in major depressive disorder, however, in an experienced hand and under close observation, MAOIs could be a potential game changer, according to Stahl, S., M. (2008) [Stahl, S., M., 2008].

Despite being a potent anti-depressant, MAOIs could theoretically lead to dangerous complications as beforementioned. MAOIs could result in an increase in tyramine after taking a diet containing higher amount of tyramine, causing tyramine reactions that could lead to a potentially lethal hypertensive crisis as tyramine is a strong releaser of norepinephrine.

According to Stahl, S., M., (2008), although, MAO-A (Mono Amino Oxidase A) could efficiently destruct tyramine contents from food, in combination with MAOIs, only 8 to 10 mg of tyramine is considered to be sufficient to induce a hypertensive crisis. Generally, a person can handle up to 400mg of tyramine without presence of MAOIs.

Although, MAOIs are highly known for their Tyramine Reaction, drug interaction of MAOIs with sympathomimetic drugs such as nasal decongestant xylometazoline and phenylephrine could prove to be even more dangerous [Stahl, S., M., 2008].

Aside from that, tyramine reaction and an upsurge in sympathomimetic action could be potentially hazardous, but a combination of MAOI and 5-HT blocker such as chlorpheniramine that could lead to serotonin syndrome, could be literally life-threatening.

According to Gillman, P., K., (2006), neurostimulators, in general, in combination with MAOIs must not be used, since MAOIs themselves exert neuro-stimulant action [Gillman, P., K., 2006].

Nevertheless, according to Krishnan, K., R., (2007), from a therapeutic point of view in case of patients with major depressive disorder who did not respond well with other antidepressants, MAOIs such as Moclobemide, an irreversible selective MAO-AI (Mono Amino Oxidase-A Inhibitor), is considered to be as effective as amitriptyline and fluvoxamine to maintain an antidepressant action up to 12 months, while it was also said to be comparatively safer, as the norepinephrine released following a high tyramine meal

would produce an inhibitory action on reversible MAOIs, hereby restoring normal MAO-A functions in the intestine. MAO-As are available in intestine and brain [Krishnan, K., R., 2007].

According to Jacob, Muller and Schmidt (2005), a rule of thumb to use irreversible MAO-BI (Mono Amino Oxidase-B Inhibitor), such as selegiline as an anti-depressant could be to use trans-dermally, as MAO-BIs had shown poor efficacy to treat depression given their low extent of noradrenergic effect, however, MAO-BI could increase the release of MAO-AI from intestine and had shown a lower risk of drug interaction. Reversible MAOIs such as phenelzine are not as effective as irreversible MAOIs to treat depression [Jacob, Muller and Schmidt, 2005].

However, unless a close observation is possible and the patient is not responding in other Antidepressant in major depressive disorders, it could be concluded that MAOIs should not be treated as a first line treatment.

2.3.6. Suicidal ideation in Antidepressant treatment

Arguments regarding suicidal ideation in antidepressant treatment, in particular in SSRIs, had begun to emerge back in the 1990s, when Teicher, Glod and Cole had found out six patients with intense suicidal ideation following fluoxetine treatment [Teicher, Glod and Cole, 1990], while a number of clinical cases and studies reporting the impacts of sertraline and paroxetine on suicidal ideation alongside akathisia had led to an observation that SSRI-induced suicidality should be considered as a class effect rather than a severe psychotic incident limited to fluoxetine, according to Lane, R., M., (1998) [Lane, R., M., 1998]. Healy, D., had written in an editorial in 1999s that an increase in suicidal ideation by SSRIs had ostensibly been demonstrated through the drugs' adverse effects, which had been demonstrated in a cascade of clinical trials, investigations from pharmaceuticals and medicolegal authorities alongside evidences from federal courts among others [Healy., D., 1999].

Furthermore, in lieu of using SSRIs, other antidepressant could potentially increase the risks of suicidal ideation, in particular SNRI and NDDI, as Wolf, D., (2005) had told in 2005 that the use of SSRI

antidepressants had been closely associated with suicidal thinking and behaviour, though the risks could be lessened using a combined CBT (Cognitive Behavioural Therapy).

Concomitantly, an increase in risk of suicidal ideation and behavioural changes in psychosis and major depressive disorder while being treated with antidepressant, had been labelled as a key black-box warning by the US FDA (Food and Drug Safety Administration), while a recommendation to screen for bipolar disorder before inducing antidepressant had also been recommended given the antidepressants' role in triggering a manic or depressive disorder in high-risk patients [Wolf, D.,2005]

Offering further evidence on suicidal ideation in treatment with antidepressant, data obtained from a clinical trial by Khan et al., (2001) and Kirch et al., (2002) had revealed incidences of suicides and suicide attempts in patients with antidepressant therapy, while the result of the trial had found that patients taking Citalopram, Mirtazapine and Paroxetine had suffered from the highest number of suicidal attempts. According to the clinical trial, percentage of suicides among the study group are mentioned below at a chronological order showing high-risk to low-risk antidepressant.

- Citalopram - 2.38%
- Mirtazapine – 1.53%
- Paroxetine – 1.52%
- Venlafaxine – 1.40%

[Khan et al., 2001; Kirch et al., 2002]

2.3.7. Anti-depressant withdrawal and potential complications leading to psychosis and depression

Withdrawal from an antidepressant medication in patients who have been treating with antidepressants over six weeks would more likely to have potential withdrawal syndromes, had those medications been withdrawn or reduced abruptly, eventually making the particular drug class more vulnerable to a public perception that antidepressant are addictive, which in effect could result a reduction in efficaciousness

considering the drugs' psychological impacts as it had been underscored in "*The Maudsley prescribing guidelines in psychiatry.,*"(2015) ['*The Maudsley prescribing guidelines in psychiatry*'., 2015].

Adding further strains, Rush et al., (2011) had highlighted that some patients might not experience a depreciation in withdrawal symptoms following dose taper, while clinical studies had been found that many patients had not been developing withdrawal symptoms at an early part of dose taper, but had been developing severe symptoms at the later stage of taper. Usually, biological activity of antidepressants persist between two to three weeks and a taper dose regimen could last up to four weeks given the patients' response. [Rush et al., 2011]

Furthermore, "*The Maudsley prescribing guidelines in psychiatry.,*" (2015) had suggested that an abrupt cessation of Antidepressant could stem a relapse or further exacerbation of illness, which might involve psychosis and major depressive disorders apart from panic attacks and severe anxiety, while such exacerbations could lead to life-threatening conditions in high-risk patient groups. Another life-threatening clinical condition, Serotonin Syndrome could occur during antidepressant withdrawals ['*The Maudsley prescribing guidelines in psychiatry*'., 2015].

2.3.8. Complications of long-term anti-depressant use

Many people across the globe are taking anti-depressant medication for a prolonged period of time. According to Pratt, Brody and Gu (2017), more than a 25 per cent Americans, who at least once had been treated with antidepressant medication, were abusing Fluoxetine and Sertraline over a decade or more. But, in an alignment with the period of antidepressant abuse, potential health risks and side effects of antidepressant usually begin to emerge [Pratt, Brody and Gu, 2017].

As there are concerns mounting among clinicians that many people are taking antidepressant medication for a longer period, findings of a meta-analysis of 17 studies conducted and published back in the 2017s in the Journal of Psychotherapy and Psychosomatics by Maslej et al., (2017), had suggested that people who used antidepressant for a longer duration might have had a 14 per cent higher risk of cardiovascular

diseases such as heart attack and stroke contemplating most antidepressants' anticholinergic effects which often involve arrythmia, tachycardia, hypertension, convulsion and an intervention in voltage gated Na+ channels among others, and a 33 per cent greater risk of death.

Moreover, SSRIs, in particular, are associated with a higher mortality rate given the serotonin receptors' involvement in critical processes such as immunity, growth and digestion [Maslej et al., 2017].

Patients having been treated with SSRIs such as Fluoxetine are highly vulnerable to develop psychosis and major depressive disorders alongside suicidal ideation, though, use of CBT (Cognitive Behavioural Therapy) could decrease the side-effects of SSIRs by a substantial scale as beforementioned, adding a silver lining to SSRI medications amid growing scrutiny.

Nonetheless, a growing number of clinicians of APA (American Psychiatric Association) had surprisingly started off suggesting longer-term antidepressant treatments, even for an indefinite period of time, despite their wide-ranging adverse effects such as heart disease, stroke and early death in elderly as underscored by Péquignot et al., (2019) [Péquignot et al., 2019], marking off a contentious act which is often being criticized.

2.4. Comparative efficacies of anti-depressants in treating Major Depressive Disorders & psychosis

In what has been viewed as a global-scale burden, psychiatric disorders accounted for a 22.8 per cent of all diseases, while depression had long been witnessed as a leading cause in developing psychiatric disorders with a jawdropping 350 million people currently suffering from depressive disorders.

According to Ioannidis, J., P., (2008), contemplating a significantly higher rate of marketing malpractice of antidepressant drug classes in the United States, more than a $210 billion had been spent in the US alone with an appalling 45 per cent related to direct costs to treat depression [Ioannidis J., P., (2008)].

Despite long-lasting debates and concerns of efficacy and effectiveness, antidepressants are widely used in treating patients with major depressive disorders, as newer generation antidepressants had shown greater efficacy to treat Schizophrenia, OCD, mood disorder, major depressive disorder alongside delusional depression among many others.

2.4.1. Efficacy of Antidepressant in Major Depressive Disorder

A systemic review on past literatures conducted by Cipriani et al. (2018) had found agomelatine, mirtazapine, venlafaxine, amitriptyline, escitalopram and paroxetine to be more efficacious than other anti-depressants in treating Major Depressive Disorders in adults and fluoxetine, reboxetine and vortioxetine had been found to be the least efficacious antidepressant [Cipriani et al., 2018].

Furthermore, back in the 1984s, Coryell, Pfohl and Zimmerman (1984) had unveiled while treating patients suffering from psychotic depression, a commoner than assumed disorder associated with depressive episodes with psychotic disorders, that antipsychotics alongside antidepressants with or without ECT (electroconvulsive therapy) could be highly effective [Coryell, Pfohl and Zimmerman, 1984].

According to Nelson, Orr and Khan (1983), TCA antidepressants had responded in treating patients with delusional and non-delusional depressions, however, an augmentation of anti-psychotic had revealed mixed responses, but tricyclic antidepressants' mode of action to treat delusional depressions remained poorly understood. Nonetheless, both delusional and non-delusional depressions had been frequently associated with family history of depressions and cortisol hypersecretion [Nelson, Orr and Khan, (1983)].

2.4.2. Efficacy of Antidepressant in psychotic disorders

According to Cardinal et al., (2015), antidepressant alone or in combination with antipsychotic drugs had shown a greater response in patients with schizophrenia, while aripiprazole, mirtazapine, venlafaxine had shown a better potency in treating schizophrenia or schizoid personality disorder [Cardinal et al., 2015].

Moreover, Ghio et al., (2011) had found a combination of SSRI Antidepressant such as Fluoxetine and atypical antipsychotics such as olanzapine highly effective in treating patients with psychotic depression in 2004 [Ghio et al., 2011].

Gartlehner et al. (2019) had shown an increased efficacy of newer generation anti-depressants in treating patients with seasonal affective disorder which is often associated with a seasonal pattern in recurrence of depressive episodes, however, the authors had not recommended the use of antidepressants but buproprion in preventing seasonal affective disorder [Gartlehner et al., 2019].

Halle et al., (2015) had depicted comparative benefits of newer generation antidepressant augmented with CBT in treating patients with major depressive disorder, while fluoxetine, fluvoxamine, sertraline, citalopram and escitalopram had been found to be effective, though the authors had orchaestrated a poor understanding of mechanism of action of a combination therapy of second-generation Antidepressant and CBT [Halle et al., 2015].

Besides, among wide-ranging somatic symptoms, Skljarevski et al., (2012) had addressed efficacy of Duloxetine in patients with somatic symptoms such as chronic low back pain [Skljarevski et al., 2012], however, Duloxetine had been associated with a number of serious side-effects such as cardiac arrythmia, hyponatraemia and hypertensive crisis among others. Moreover, Wang, Sun, and Wang (2012) had treated functional chest pain with no underlying cardiovascular abnormality with antidepressants [Wang, Sun, and Wang, 2012]. Uzun and Ozdemir (2010) had recommended a combination of fluvoxamine and aripiprazole in treatment-resistant body dysmorphic disorder [Uzun and Ozdemir, 2010]. Fuchs, T., (1992) had found an augmentation of antidepressant with antipsychotic to be efficacious in treating hypochondriac delusion [Fuchs, T., 1992].

2.5. Complication, tolerability, safety of newer generation anti-depressants

As beforementioned, antidepressants are found to be potentially effective in treating schizophrenia, schizoid personality disorders and psychotic major depressions.

Furthermore, as antidepressant medication such as TCAs in patients with Bipolar Disorder could cause potential side-effects, in treatment of bipolar patients, newer generation antidepressants are widely used, mostly in primary healthcare facilities. Newer generation antidepressants had revealed greater efficacy in patients with Multiple somatoform syndrome alongside somatic symptoms such as body dysmorphic disorders and hypochondriasis.

Newer generation antidepressants are usually considered safer than TCAs in treatment of major depressive disorders, though newer generation antidepressants such as SSRIs, SNRIs, mirtazapine, agomelatine, Levomilanacipran, vilazodone, trazodone and bupropion have been associated with considerable scale of risks, hence requiring further monitoring and screening following induction of treatment.

According to a systemic review of existing scientific journals and relevant works conducted by Carvalho at el., in 2016, minor adverse effects of newer generation antidepressants might include gastric irritation and minor anticholinergic symptoms alongside reversible sexual dysfunction, while potentially more dangerous side-effects might include hepatotoxicity, hypersensitivity reactions, dermatological manifestations, cardiovascular diseases, osteoporosis, cataract, glaucoma, teratogenicity, malignancy and hyponatraemia among others. .

Besides, all newer generation antidepressants could lead to psychosis and depressive disorders, though, SSRIs, in particular, are associated to affective or mood disorder, suicidal ideation, serotonin syndrome, unipolar mood disorder and psychotic depression among others [Carvalho at el., 2016].

Apart from that, contradicting a finding by Kirsch et al., (2008), who had found antidepressants to be effective in severely depressed patients [Kirsch et al., 2008], Vöhringer and Ghaemi (2011) had found antidepressants to be less effective in mild depressive episodes, but more efficacious in treating patients with acute depressive disorders, which mirrored a majority of past research studies' findings [Vöhringer and Ghaemi, 2011].

Moreover, according to Steward, Deliyannides and Hellerstein (2012), antidepressants could be highly effective to treat mild to moderate major depressive disorders [Steward, Deliyannides and Hellerstein, 2012]. Thorlund, Druyts and Wu (2015) had been quoted saying in a meta-analysis of use of SSRI and SNRI in patients aged above 60, “The authors found…clear evidence of the effectiveness of sertraline, paroxetine, and duloxetine” [Thorlund, Druyts and Wu, 2015].

2.5.1. Benefits & complications of TeCAs/NaSSAs (Mirtazapine)

NaSSAs (Noradrenergic and Specific Serotonergic Antidepressants) are primarily used as anti-depressants which at the same time, block some serotonin receptors such as 5-HT2A, 5-HT2C, 5-HT3, 5-HT6, and/or 5-HT7 and exert serotonergic effects on others, thereby preventing a swathe of side effects of SSRIs, suggested Robert, M., (2004) [Robert, M., 2004]. Concomitantly, according to Robert et al., (2009), NaSSAs antagonizes alpha-2 adrenergic auto-receptors, however, excels adrenergic and serotonergic functions in the brain and widely used in mood regulation [Robert et al., 2009].

Mirtazapine has been the most widely used NaSSAs, however, aptazapine, esmiratazapine, mianserin and setiptiline are also considered as NaSSAs.

Though, according to Millan et al., (2012), those NaSSAs could also be categorized as TeCAs (tetracyclic) considering their chemical structures. Apart from averting potential side effects of SSRIs, a structurally novel NaSSA would not be exerting any anti-histamine effect, hence increasing patient compliance level [Millan et al., 2012].

2.6. Safety and tolerability of newer generation anti-depressants in children and adolescents

Some newer generation antidepressants had shown a better response against psychosis and depression in children and adolescents in comparison to TCA Antidepressant as beforementioned.

However, Gibson et al., (2012), had found that the newer generation Antidepressant had been effective to treat major depressive disorders in youth and adolescence in short term. Besides, suicidal thoughts and behaviour had developed in children who had been treated with fluoxetine and venlafaxine, however, no such incidences were associated in a youth age group [Gibson et al., 2012].

Moreover, in order to gauge the risk-benefit ratio of an antidepressant, in particular SSRIs for child and adolescent, evidences supporting the medicinal provocation of suicidal thought along with unveiling any kind of untreated depressions are utterly important, according to American Psychological Association (APA)., (2006) [American Psychological Association, 2006], as often antidepressants could exacerbate underlying depressions, although, mechanisms of which remained poorly understood.

However, data from past studies had unveiled had revealed that there had been an in increase in risks of self-inflicted harm in patients who had been receiving fluoxetine, while patients receiving fluoxetine without CBT are more prone to experience a suicidal event.

Nonetheless, Lock et at., (2005), had found in a study that about 61 per cent adolescences treated with fluoxetine had experienced a reduction in their depressive disorders, hence the initial choice of antidepressant for young and adolescents should be the newer antidepressants including SSRI and SNRI, which are highly effective to treat major depressive disorder and Bipolar Disorder in augmentation with CBT.

However, those benefits might be associated with a higher risk of developing suicidal ideation and other adverse effects such as violence and injury to self and others [Lock et al., 2005].

Cipriani A., (2016) had suggested that fluoxetine could be the most effective SSRI for child and adolescents [Cipriani A., 2016].

Besides, Walkup et al., (2008) had told in a study that a combination therapy of sertraline and CBT did not prompt suicidal ideation in young adults who had been suffering from anxiety disorders, nonetheless,

the study could not reveal whether sertraline had been effective to reduce depression in child and adolescent [Walkup et al., 2008].

Therefore, it could be said that the newer generation antidepressant could be effective to treat mild to moderate depression and psychotic events such as unipolar depression, but, their efficacies to treat major depressive disorder remained subject to sheer discontent. In order to ensure safety in a child and adolescent having been contemplated for antidepressant medication, must be screened whether the patient had underlying Bipolar Disorder or depression, while children and adolescents having treated with a newer generation antidepressant should be in close observation until a conclusive response and CBT could be added to decrease the chances of developing suicidal thoughts, violence and mania.

2.7. Case studies of Antidepressant induced psychosis and depressive disorders

Antidepressants have been frequently documented as a potent inducer of psychotic disorders and mania since their inception back in the 1950s as beforementioned.

2.7.1. SSRI induced mania, psychosis, violence, personality disorders and suicidal ideation in patients with psychotic illness and depressive disorders

Preda et al., (2001) had found in a retrospective study that about 8.2 per cent patients had been admitted following antidepressant-induced psychosis or mania among 533 consecutive admissions into the adult psychiatric inpatient service Yale-New Haven Hospital between January 1, 1997 and February 28, 1998, while the patient inclusion criteria had been exacerbation of psychotic or manic symptoms, antidepressant use during admission, use of antidepressant within past four months of admission and improvement

following discontinuation of antidepressant therapy or replacing antidepressant with a mood stabilizer. The Study group's mean age had been 38±8(standard deviation) years and the study included 226 male and 307 female patients. An 8.2 per cent of study group or 43 patients who had developed antidepressant induced psychotic illness and mania, had had a mean age of 'onset of illness' of 22±11(SD) years and their mean duration of illness had been 14±9(SD) years [Preda et al., 2001].

Dorevitch et al., (1993) had reported three separate cases of fluvoxamine-induced mania, while discontinuation of associated antidepressant had promptly stopped the symptoms. Moreover, despite three cases of violence and aggressive behaviour in patients in fluvoxamine treatment with all of them taking 150 mg per day of fluvoxamine, all three patients showed signs of improvement after discontinuation of drug [Dorevitch et al., 1993]. According to a case report stated by Bastani et al., (1996), a woman having been treated with fluvoxamine for depressive symptoms became suicidal, however, the patient had recovered in less than 24 hours after cessation of the antidepressant treatment [Bastani et al., 1996].

Lipinski et at. (1989) had reported five cases of akathisia following induction of fluoxetine, while a literature reviewed by Lipinski (1989) had found out that fluoxetine could yield akathisia in about 9.7 per cent to 25 per cent patients being treated with fluoxetine [Lipinski et al., 1989]

According to case studies conducted by Rothchild and Locke (1991), fluoxetine-induced suicidality and akathisia had been stopped following cessation of the drug [Rothchild and Locke, 1991].

2.7.2. Discontinuation of Antidepressant in newly admitted psychotic patients

Malcom et al., (2003) had found in a retrospective study that 16 consecutive patients (12 females and 4 males) aged between 22 and 69 years who had been treated with antidepressant due to psychosis as well as depression and admitted into the hospital after developing psychotic illness or mania, had experienced a mean decrease in 18 criteria Brief Psychiatric Rating Scale (BPRS) [Please see Appendix D] by 18.6 ±

10.1 (SD) points following immediate discontinuation of antidepressant after 4 to 7 days (mean 4.7) of admission, while the inclusion criteria had been manic or psychotic symptoms, medication compliance before admission alongside a treatment regiment during admission that involved an antidepressant along with a mood stabilizer or antipsychotic. DSM IV [Please see Appendix E, F, I] diagnostic criteria of the subjects had found 5 patients with psychosis, 1 patient with BD with psychosis, 3 patients with schizoaffective disorder, 5 patients with schizophrenia and 2 patients with psychosis. Before hospital admission, the study groups' mean BPRS score had been 50.5 ± 11.1 (SD) [Malcom et al., 2003].

2.7.3. Antidepressant induced mania and bipolar disorder in patients with depression

Furthermore, Patel et al. (2005) had found in a retrospective cohort study that among a total of 21,012 patients aged between 16 and 35 with unipolar depressions and no history of prior mania or bipolar disorder, registered in a SLaM health database between April 1, 2006 and March 31, 2013, about 13.1 to 19.1 per 1000 patients/ year had developed mania or bipolar disorder, while the inclusion criteria included treatment with Antidepressant and the peak age group developing bipolar disorder or mania had been between 26 and 35 years. However, SSRIs and venlafaxine, an atypical antidepressant, had shown a substantial scale of risk [Patel et al., 2015].

2.7.4. Antidepressant induced mood switch in bipolar disorder & TCA induced anti-cholinergic symptoms

Koszewska and Rybakowski had found in 2009 in a retrospective cohort study that among a total of 333 Bipolar Disorder patients, 193 females and 130 males, being treated with Antidepressant between 1972 and 1996 in the Institute of Psychiatry and Neurology, Warsaw, 118 patients (35 per cent) had experienced mood conversion (mania) during hospitalization, while the inclusion criteria included

patients with bipolar disorder and antidepressant treatment according to ICD-IX criteria of Bipolar Disorder alongside DSM-IV symptomatic criteria for manic episodes [Please see Appendix I] had been contemplated having a duration of at least four days. The 118 patients with Bipolar Disorder who had developed mood conversion while being treated with AD, 85 patients were female and 33 were male, while their mean age had been 55 ± 14(SD) years and mean age of the patients who had not developed mood conversion, had been 55 ± 13(SD). In addition, among 118 patients who had suffered moon conversion, there had been 371 depressive episodes and 323 of them had been treated with Antidepressant. A 65 per cent of those 323 episodes, which had been treated with 534 antidepressant drugs in total, had turned to mania [Koszewska and Rybakowski, 2009]. According to El Fakahany and Richelson (1983), Further evidences unfolded that TCA-induced mania increased the risks of psychotic episodes, while mood conversions took place most frequently in the patients having treated with amitriptyline (42 per cent), imipramine (40 per cent), clomipramine (35 per cent).

TCA-Antidepressant' anti-cholinergic symptoms exerted through specific muscarinic receptor affinity are thought to be responsible behind the mood conversions as beforementioned. Likewise, TCA-induced delirium and exacerbation of psychotic events following use of TCA antidepressants are mostly because of their anti-cholinergic mode of actions.

3.0. Research methodology

Since this has been a 'literature review'-based argumentative research, past studies on risks of antidepressant-induced psychotic events in patients with depression and psychosis have been dissected with an exhaustive approach, while the literature review section also had highlighted multiple case studies and metal-analysis related to antidepressant-induced psychotic events requiring hospital admissions. However, the segment has underscored benefits of newer generation antidepressants which in effect could reduce the chances of developing potential side-effects. Considering the cerulean efficacy of MAOIs in major depressive disorders in adult patients, who had not responded well during their first-line antidepressant medication, a review of past research works on benefits of using MAOIs had been conducted despite their wide-ranging drug interactions.

3.1. Data collection and analysis

Being a literature review-based argumentative research paper, in order to identify the risks of anti-depressant induced psychotic events in patients with depression and psychosis, this paper had vigorously analysed past works regarding threats associated with antidepressant treatment. In a bid to reach an insightful conclusion, this paper had contemplated both risks and benefits of use of antidepressants in patients suffering from psychosis and depression and conducted an elaborative argument on whether the benefits could outweigh the risks of developing antidepressant-induced psychotic episodes and depressive illness, findings of which are unveiled on results.

4.0. Results: Findings, Arguments & Recommendations

This literature review-based argumentative research had analysed past works on risks of antidepressant-induced psychosis and depressive disorders. On numerous occasions, antidepressants are found to be stemming complications, however, their benefits might have outweighed the risks with proper monitoring.

In this particular section, findings of previous works would be discussed and an argument would be conducted based on the findings to reach a deduction on whether the risks of antidepressant-induced psychotic events and depressive disorders could eclipse associated risks and adverse effects.

4.1. Findings & arguments

Despite widespread use of TCA and non-TCA antidepressants in psychotic events or depressive symptoms, a number of past studies had found out TCA induced anti-cholinergic symptoms which could have been life-threatening in certain cases, if the symptoms remained unaddressed, however, a cessation of treatment had stopped the symptoms.

Past studies had suggested that patients had developed acute mania in combination therapy of SSRIs such as venlafaxine and TCAs, however, use of other newer antidepressants such as mirtazapine had decreased the risks.

Besides, antidepressants that could be used as an antiparkinsonian agent such as MAO B inhibitors (Selegiline) had unveiled an increase in risk of developing both auditory and visual hallucinations alongside acute psychosis, though a switch to another group of drugs had stopped the complications.

Antidepressant induced switching to mania in patients with BD had been reported in several past studies, while previous studies and meta-analysis of literatures had reported more than a 33 per cent with BD had developed mood switch while being treated with Antidepressant, and about 36 per cent and 17 per cent patients might develop mood switch with TCA Antidepressant and SSRIs respectively. Treating unipolar

major depressions using TCA Antidepressant could exacerbate risks of delusional depression or psychotic depression in some cases, however, a switch to another class of drug such as NaSSAs (Mirtazapine) had stopped the symptoms. Besides, it has been found to be important to screen a patient for underlying BD or depression before starting antidepressant, as antidepressants could exaggerate risks of developing mania in patients with bipolar as beforementioned.

Long-term use of a combination therapy of Antidepressant-antipsychotics in patients with schizophrenia or related psychotic disorders, had increased the risks of developing TCA-induced anti-cholinergic symptoms, nonetheless, use of another class of drug had stopped the symptoms. Though, schizophrenic patients would more likely to suffer from antidepressant adverse effects considering the treatments' long duration.

Furthermore, SSRIs are often linked to conceiving suicidal ideation, violence, mania, personality disorder and psychosis apart from serotonin syndrome in SSRIs with serotonergic functions, while instead of using SSRIs, use of other Antidepressant such as SNRI as well as NDDI could decrease the risk of suicidal ideation. Besides, a combination of SSRIs and CBT had decreased the risks of developing suicidal ideation and violence in all age groups.

Abrupt withdrawal or cessation of Antidepressant could lead to a relapse or further exacerbation of symptoms involving psychotic episodes and major depressive disorders, while withdrawal effects of Antidepressant could stem a misinterpretation that antidepressant are addictive, which in effect could decrease patient compliance.

Patients with long-term use of antidepressant who should not be taking antidepressants, could experience a higher risk of cardiovascular disorders, in particular with TCA antidepressant, while complications in immunity, growth and digestion had been found to have close relation with long term use of SSRIs.

Furthermore, newer generation Antidepressant such as Fluoxetine had been found to be causing suicidal ideation and violence in child and young adults, however, a combination of fluoxetine with CBT had

diminished the risks of developing suicidal ideation and violence. Besides, often past studies had referred to Fluoxetine as the first line of treatment to treat major depressive disorders in child and young adults.

Looking at the flipside, many studies had found Antidepressant alone or in combination with antipsychotic medication had shown a greater response in patients with schizophrenia or schizoid personality disorders. In treating psychotic or delusional depression, a combination of SSRIs and olanzapine had been found to be highly efficacious.

Seasonal affective disorders which were non-responsive to traditional Antidepressant, had responded particularly well while being treated with buproprion.

In treating major depressive disorder, newer generation Antidepressant along with CBT had been found to be highly efficacious with a lower risk of adverse effects, duloxetine shows a higher response in treating major depressive disorder.

Duloxetine had shown efficacy in treatment of patients with acute or chronic back pain without steroids, while other somatic symptoms such as treatment resistant body dysmorphic disorder and hypochondriasis had responded in treatment with fluvoxamine and aripiprazole combination.

Despite MAOIs wide-ranging drug interactions such as tyramine reaction, exacerbation of sympathomimetic action when induced with decongestants and serotonin syndrome when induced in combination with chlorpheniramine, low-risk monoamine oxidase inhibitors such as moclobemide are often considered as a secret weapon in treating major depressive disorder, panic disorder, anxiety disorder and social phobia.

4.2. Controversies

Looking at the flipside, many past studies had highlighted the importance of using Antidepressant in depression and psychosis contemplating that their benefits could outweigh the risks, while there had been conflicting findings on several studies including a study conducted by Kirch et al., (2008) which had found all classes of Antidepressant had been effective in severely depressive symptoms [Kirch et al.,

2008]. Controverting the finding of Kirsch et at., Vohringer and Ghaemi (2011) had told that antidepressants could be more effective in mild to moderate depression [Vohringer and Ghaemi, 2011]. Besides, there had been controversies about use of SSRIs and SNRIs, as contradicting the finding of several past studies that had cited a growing risk of use of SSRIs and SNRIs in patients above 60 in psychosis and depression including fall and fracture alongside other adverse effects of newer generation antidepressants, it was found in a meta-analysis of past studies that the risks associated with SSRIs and SNRIs such as sertraline, paroxetine and duloxetine in elderly had clearly outweighed the benefits.

Furthermore, a number of past studies had mentioned an increase in risk of bias in research-based evidences in patients having been treated with antidepressant, while major underlying psychotic and depressive disorders remained unaddressed in most cases in outpatient departments across many countries in the globe, thereby raising the risks of an exacerbation of underlying disorders while being treated with antidepressants.

All antidepressants could cause mania and mania has been a well-acknowledged side effects of most US FDA approved antidepressants.

4.3. Recommendations

Followed by a review of the findings and controversies, it could be summarized that most antidepressants are associated with developing psychotic or depressive disorder, however, the risk of antidepressant-induced psychosis and depressive illness could not rule out the benefits, if they could be induced following proper history taking with precise observation as well as thorough follow-up.

While contemplating tricyclic antidepressants, this particular drug class could cause delusional depression in unipolar depression, a mood disorder, and anti-cholinergic symptoms in treating depressive disorders, however, the complications could be averted by replacing the drug class.

MAOIs are linked with higher drug interaction, hence its benefits could not dwarf the risks and should be considered as a last line of defence in major depressive disorder.

Neurotransmitter reuptake inhibitors such as SSRIs and SNRIs are the most prescribed antidepressants in many countries, especially in OPD (Out Patient Department), though, ironically, those could lead to the highest number of complications as well. SSRIs with serotonergic mode of action such as agomelatine and fluvoxamine could lead to serotonin syndrome, while MAOIs in combination with certain antihistamines such as chlorpheniramine could cause serotonin syndrome. However, SSRIs also elicit symptoms of personality disorder, mood switch in BD, self-harm, violence, suicidal ideation, mania, psychosis and personality disorder.

Nevertheless, SSRIs such as fluoxetine is often contemplated as one of the most effective drugs to treat major depressive disorder, though there are controversies and adverse effects, while an SNRI, Venlafaxine, had been found to be more effective to treat schizophrenia in combination of olanzapine. Duloxetine, an SNRI, is found to be effective in treating MDD in elderly and multiple somatoform symptoms including low back pain with patients not being treated with corticosteroid. Buproprion, an NDDI, could be potent to treat seasonal affective (mood) disorder.

Besides, most SSRIs, SNRIs and NDDIs induced side effects could be averted by a combination of CBT.

On top of that, in case of SSRI-tolerant major depressive disorders and mood disorders, mirtazapine, an NaSSA, had been found to be efficacious.

Nevertheless, there had been controversies in past literatures on efficacies of TCA and SSRIs to treat major depressive disorder, while TCAs were said to be less effective than SSRIs to treat mild to moderate depressive disorders, while none of them but fluoxetine and MAOIs had shown a higher efficacy in treating major depressive disorders. Though, this limitation could be overcome by using newer generation Antidepressant which had shown a greater response against major depressive disorders.

Thereby, contemplating the risks of antidepressant-induced psychotic events in patients with depression and psychosis, it could be said that the benefits of Antidepressant could outweigh the risks in presence of proper history taking, monitoring and follow-up in all age group, as Hammand, Laughren and Racoosin

(2006) had said that evidences suggested that the benefits of Antidepressant use in child and adolescent could offset risks [Hammand, Laughren and Racoosin, 2006].

5.0. **Limitation & biasness of available researches**

There are many practical as well as theoretical problems associated to the ways past Antidepressant studies had been conducted, as the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [Please see Appendix I.] had underscored marked differences in findings of past studies that discussed the relationship between degree of depressive disorders and Antidepressant drug class efficacy.

Walsh, Seidman and Sysko, (2002) had found an increase in rate of placebo response in patients with depressive disorders and [Walsh, Seidman and Sysko,2002] had underscored problems and limitations associated to all meta-analyses of previously conducted studies.

Adding further holocaust, findings of a past study would highly likely to depend on which scale is used for assessment of data. For instance, using HAMD (Hamilton Depression Scale) [Please see Appendix C.], Gibbons, Hur and Brown (2012) had found a combination of fluoxetine and venlafaxine highly effective in treating acute symptoms of major depression in all age groups, contradicting the US FDA's black-box level of risk of use of Antidepressant in child and young adult [Gibbons, Hur and Brown (2012)]. Concomitantly, opposing the findings of Gibbons, Hur and Brown (2012), Vohringer and Ghaemi (2011) had found antidepressant medications' efficacy in only acute depressive disorders in patients with mild to moderate depressions [Vohringer and Ghaemi, 2011].

Moreover, according to Bagdy, Ryder and Schuller (2004), a study would depend mostly on which version of HAMD or HAMD item clusters are used [Please see Appendix D] and HAMD might not be a gold standard of using Antidepressant response given the use of other scales such as Montgomery-Asberg

Depression Rating Scale (MADRS), Zung Self-Rating Depression Scale alongside Beck Depression Inventory among others [Bagdy, Ryder and Schuller, 2004].

Furthermore, inclusion of patients with less severe depressive illness remained a major as cited by Bridge et al. (2009) [Bridge et al., 2009].

Nonetheless, considering the limitations, it could be concluded in contrast to this particular literature review-based argumentative study that the previously conducted randomized and controlled research works have unveiled the newer generation antidepressant are modestly effective and generally safe, though many problems appear to have continued to complicate research literatures including publication bias.

6.0. Conclusion

The safety profiles of use of atypical and newer generation antidepressants apart from TCAs have led to a widespread increase in use of antidepressant drugs across the globe, which in effect also had raised concerns to a growing likelihood of experiencing adverse effects of therapeutic use of antidepressants. This 'literature review'-based study aims to analyse the risks and extent of risks of use of antidepressants given their widespread insinuations in patients with psychotic and depressive disorders despite growing evidences of antidepressant induced psychosis and major depressive disorders ranging from depression to bipolar, unipolar or mood disorders to schizophrenia and multiple somatoform disorders among others. Apart from that, people with unipolar depression, antidepressant treatments were found to be associated with a higher risk of developing bipolar disorders. Besides, safety of anti-depressants' use in child and adolescents remained subjected to an utter dubitability, while a number of previous research works had underscored the risks of developing psychotic events in use of antidepressants in people with or without potential risk factors.

Nevertheless, although a lion's share of anti-depressant induced psychotic events are associated with the use of SSRI and SNRI, several previous works had highlighted the benefits and a better safety profile of

newer generation Antidepressants, as fluoxetine has often been touted as the most effective anti-depressants, while MAOIs could act as a potent second-line treatment option for patients who had not responded well on their first-line therapy. SSRI-induced mania, violence and suicidal ideation could be decreased dramatically by augmenting CBT into the treatment, while other newer generation drugs such as venlafaxine could be an excellent treatment option for treating Schizophrenia in combination with atypical antidepressants such as olanzapine or clozapine. Mirtazapine (NaSSAs) is often used as a mood stabilizer, while Duloxetine (SNRI) had shown a better efficacy to treat major depressive disorders. Bupropion (NDRI) has been a well-acknowledged treatment option for seasonal affective disorder. Besides, Moclobemide (MAOI) could be a potent antidepressant compound to treat major depressive disorders which do not respond at their first line of treatments. Along with other noradrenergic (Trazodone) and serotonergic (Manserine) medications, Doxepin had shown a better efficacy in treating bipolar disorders, while a melanin receptor agonist, agomelatine showed better efficacy in as a potential drug to treat major depressive disorders.

Followed by a conceivably competitive breakdown of benefits and risks of antidepressants in patients with psychosis and depressive disorders, it could be perceived that the risks of antidepressant-induced psychotic events and depressive disorders could be overshadowed by the benefits in a comeliest coexistence of a punctilious history taking, precise monitoring and apposite follow-up in patients who are being contemplated for antidepressant therapy.

7.0. References

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8.0 **Appendix**

A. Primary DSM IV depression criteria for adults

Depressive Diagnoses	Symptoms
Major Depressive Episode: - 5 or more depressive symptoms for ≥ 2 weeks - Must have either depressed mood or loss of interest/pleasure - Symptoms must cause significant distress or impairment - No manic or hypomanic behavior ***Minor Depressive Episode:**** - 2–4 depressive symptoms for ≥2 weeks - Must have either depressed mood or loss of interest or pleasure - Symptoms must cause significant distress or impairment - No manic or hypomanic behavior	1. Depressed Mood 2. Markedly diminished interest or pleasure in most or all activities 3. Significant weight loss (or poor appetite) or weight gain 4. Insomnia or hypersomnia 5. Psychomotor retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive or inappropriate guilt 8. Diminished ability to think or concentrate, or indecisiveness 9. Recurrent thoughts of death (not just fear of dying), or suicidal ideation, plan, or attempt
Dysthymic Disorder - Depressed mood for most of the time for at least two years - Presence of 2 or more of symptoms of dysthymia - Never without symptoms for 2 months or more over 2 year period - Symptoms must cause clinically significant distress or impairment - No major depressive disorder in first two years, no manic, hypomanic, or mixed episodes.	1. Significant weight loss (or poor appetite) or weight gain 2. Insomnia or hypersomnia 3. Fatigue or loss of energy 4. Low self-esteem 5. Diminished ability to think or concentrate, or indecisiveness 6. Feelings of hopelessness

B. DSM-IV depression criteria for children and young adults

A. Depressive Diagnoses	B. Symptoms
Major Depressive Episode:	1. Depressed mood or irritability

for ≥ 2 weeks

- Must have either depressed mood or loss of interest or pleasure
- Symptoms must cause significant distress or impairment
- No manic or hypomanic behavior

Minor Depressive Episode:

- 2–4 depressive symptoms from column B for ≥ 2 weeks
- Must have either depressed mood or loss of interest or pleasure
- Symptoms must cause significant distress or impairment
- No manic or hypomanic behavior

C

activities

3. Significant weight loss (or poor appetite) or weight gain, or failure to gain appropriate weight
4. Insomnia or hypersomnia
5. Psychomotor retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness
9. Recurrent thoughts of death (not just fear of dying), or suicidal ideation, plan, or attempt

Dysthymic Disorder:

- Depressed mood or irritability for most of the

1. Significant weight loss (or poor appetite) or weight gain, or failure to gain appropriate weight

3 SUICIDE
0 |__| Absent.
1 |__| Feels life is not worth living.
2 |__| Wishes he/she were dead or any thoughts of possible death to self.
3 |__| Ideas or gestures of suicide.
4 |__| Attempts at suicide (any serious attempt rate 4).

4 INSOMNIA: EARLY IN THE NIGHT
0 |__| No difficulty falling asleep.
1 |__| Complains of occasional difficulty falling asleep, i.e. more than ½ hour.
2 |__| Complains of nightly difficulty falling asleep.

5 INSOMNIA: MIDDLE OF THE NIGHT
0 |__| No difficulty.
1 |__| Patient complains of being restless and disturbed during the night.
2 |__| Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

6 INSOMNIA: EARLY HOURS OF THE MORNING
0 |__| No difficulty.
1 |__| Waking in early hours of the morning but goes back to sleep.
2 |__| Unable to fall asleep again if he/she gets out of bed.

7 WORK AND ACTIVITIES
0 |__| No difficulty.
1 |__| Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.
2 |__| Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
3 |__| Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
4 |__| Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

8 RETARDATION (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)
0 |__| Normal speech and thought.
1 |__| Slight retardation during the interview.
2 |__| Obvious retardation during the interview.
3 |__| Interview difficult.
4 |__| Complete stupor.

9 AGITATION
0 |__| None.
1 |__| Fidgetiness.
2 |__| Playing with hands, hair, etc.
3 |__| Moving about, can't sit still.
4 |__| Hand wringing, nail biting, hair-pulling, biting of lips.

10 ANXIETY PSYCHIC
0 |__| No difficulty.
1 |__| Subjective tension and irritability.
2 |__| Worrying about minor matters.
3 |__| Apprehensive attitude apparent in face or speech.
4 |__| Fears expressed without questioning.

11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:
gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching
cardio-vascular – palpitations, headaches
respiratory – hyperventilation, sighing
urinary frequency
sweating
0 |__| Absent.
1 |__| Mild.
2 |__| Moderate.
3 |__| Severe.
4 |__| Incapacitating.

12 SOMATIC SYMPTOMS GASTRO-INTESTINAL
0 |__| None.
1 |__| Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
2 |__| Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13 GENERAL SOMATIC SYMPTOMS
0 |__| None.
1 |__| Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
2 |__| Any clear-cut symptom rates 2.

14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances)
0 |__| Absent.
1 |__| Mild.
2 |__| Severe.

15 HYPOCHONDRIASIS
0 |__| Not present.
1 |__| Self-absorption (bodily).
2 |__| Preoccupation with health.
3 |__| Frequent complaints, requests for help, etc.
4 |__| Hypochondriacal delusions.

16 LOSS OF WEIGHT *(RATE EITHER a OR b)*

a) According to the patient:	b) According to weekly measurements:
0 |__| No weight loss.	0 |__| Less than 1 lb weight loss in week.
1 |__| Probable weight loss associated with present illness.	1 |__| Greater than 1 lb weight loss in week.
2 |__| Definite (according to patient) weight loss.	2 |__| Greater than 2 lb weight loss in week.
3 |__| Not assessed.	3 |__| Not assessed.

17 INSIGHT
0 |__| Acknowledges being depressed and ill.
1 |__| Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 |__| Denies being ill at all.

Total score: |__|__|

D. 18-Item BPRS (Brief Psychiatric Rating scale)

BRIEF PSYCHIATRIC RATING SCALE (BPRS)

Please enter the score for the term which best describes the patient's condition.

0 = not assessed, 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe

1. **SOMATIC CONCERN** Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not.	SCORE ☐	10. **HOSTILITY** Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety, nor somatic complaints. (*Rate attitude toward interviewer under "uncooperativeness"*).	SCORE ☐
2. **ANXIETY** Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms.	SCORE ☐	11. **SUSPICIOUSNESS** Brief *(delusional or otherwise)* that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.	SCORE ☐
3. **EMOTIONAL WITHDRAWAL** Deficiency in relating to the interviewer and to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation.	SCORE ☐	12. **HALLUCINATORY BEHAVIOR** Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.	SCORE ☐
4. **CONCEPTUAL DISORGANIZATION** Degree to which the thought processes are confused, disconnected, or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning.	SCORE ☐	13. **MOTOR RETARDATION** Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on the basis of patient's subjective impression of own energy level.	SCORE ☐
5. **GUILT FEELINGS** Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses.	SCORE ☐	14. **UNCOOPERATIVENESS** Evidence of resistance, unfriendliness, resentment, and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation.	SCORE ☐
6. **TENSION** Physical and motor manifestations of tension "nervousness", and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.	SCORE ☐	15. **UNUSUAL THOUGHT CONTENT** Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes.	SCORE ☐
7. **MANNERISMS AND POSTURING** Unusual and unnatural motor benavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.	SCORE ☐	16. **BLUNTED AFFECT** Reduced emotional tone, apparent lack of normal feeling or involvement.	SCORE ☐
8. **GRANDIOSITY** Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation.	SCORE ☐	17. **EXCITEMENT** Heightened emotional tone, agitation, increased reactivity.	SCORE ☐
9. **DEPRESSIVE MOOD** Despondency in mood, sadness. Rate only degree of despondency; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints.	SCORE ☐	18. **DISORIENTATION** Confusion or lack of proper association for person, place or time.	SCORE ☐

E. DSM IV & DSM V criteria for mania

DSM-IV Criteria	DSM-5 Criteria
Name: Bipolar I Disorder Single Manic Episode	**Name: Bipolar I Disorder Manic Episode**
Class: Bipolar Disorders	Class: Bipolar and Related Disorders
A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).	A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently goal-directed behavior or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:	B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms have persisted (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
1. Inflated self-esteem or grandiosity	1. Same
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)	2. Same
3. More talkative than usual or pressure to keep talking	3. Same
4. Flight of ideas or subjective experience that thoughts are racing	4. Same
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)	5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation	6. Same
7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)	7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The symptoms do not meet criteria for a mixed episode.	Dropped
D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.	C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism). Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar I disorder.	D. The episode is not attributable to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or another medical condition. Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and therefore a bipolar I diagnosis.

F. DSM-IV & DSM-V criteria for Schizophrenia

DSM-IV	DSM-5
Disorder Class: Schizophrenia and Other Psychotic Disorders	Disorder Class: Schizophrenia Spectrum and Other Psychotic Disorders
A. *Characteristic symptoms*: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):	A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
1. delusions	
2. hallucinations	
3. disorganized speech (e.g., frequent derailment or incoherence)	1–4. SAME
4. grossly disorganized or catatonic behavior	
5. negative symptoms (i.e., affective flattening, alogia, or avolition)	5. Negative symptoms (i.e., diminished emotional expression or avolition).
Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.	
B. *Social/occupational dysfunction*: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).	B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
C. *Duration*: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).	C. SAME
D. *Schizoaffective and Mood Disorder exclusion*: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.	D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
E. *Substance/general medical condition exclusion*: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.	E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
F. *Relationship to a Pervasive Developmental Disorder*: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).	F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

G. DSM-IV & DSM-V criteria for Major Depressive Disorder

Paranoid Type (295.30): A type of Schizophrenia in which the following criteria are met: A. Preoccupation with one or more delusions or frequent auditory hallucinations. B. None of the following is prominent: disorganized speech, disorganized or catatonic behavior, or flat or inappropriate affect.	DROPPED
Disorganized Type (295.10): A type of Schizophrenia in which the following criteria are met: A. All of the following are prominent: 1. disorganized speech 2. disorganized behavior 3. flat or inappropriate affect B. The criteria are not met for Catatonic Type.	DROPPED
Catatonic Type (295.20): A type of Schizophrenia in which the clinical picture is dominated by at least two of the following: 1. motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor 2. excessive motor activity (that is apparently purposeless and not influenced by external stimuli) 3. extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism 4. peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing 5. echolalia or echopraxia	DROPPED
Undifferentiated Type (295.90): A type of Schizophrenia in which symptoms that meet Criterion A are present, but the criteria are not met for the Paranoid, Disorganized, or Catatonic Type.	DROPPED
Residual Type (295.60): A type of Schizophrenia in which the following criteria are met: A. Absence of prominent delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior. B. There is continuing evidence of the disturbance, as indicated by the presence of negative symptoms or two or more symptoms listed in Criterion A for Schizophrenia, present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).	DROPPED

H. DSM-IV & DSM-V criteria for OCD

DSM-IV	DSM-5
Disorder Class: Anxiety Disorders	Disorder Class: Obsessive-Compulsive and Related Disorders
Either obsessions or compulsions:	Presence of obsessions, compulsions, or both:
Obsessions as defined by (1),(2), (3) and (4):	*Obsessions are defined by (1) and (2):*
1. Recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress.	1. Recurrent and persistent thoughts, urges or images that are experienced, at some time during the disturbance, as intrusive, unwanted, and that in most individuals cause marked anxiety or distress.
2. The thoughts, impulses, or images are not simply excessive worries about real-life problems.	DROPPED
3. The person attempts to ignore or suppress such thoughts, impulses, or images or to neutralize them with some other thought or action.	2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some thought or action (i.e., by performing a compulsion).
4. The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as with thought insertion).	DROPPED
Compulsions as defined by (1) and (2):	*Compulsions are defined by (1) and (2):*
1. Repetitive behaviors (e.g., hand washing, ordering checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to the rules that must be applied rigidly.	1. SAME
2. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation. However, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive.	2. SAME
At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable.	DROPPED
The obsessions and compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.	The obsessions or compulsions are time consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an eating disorder, hair pulling in the presence of trichotillomania; concern with appearance in the presence of body dysmorphic disorder: preoccupation with drugs in the presence of a substance use disorder: preoccupation with having a serious illness in the presence of hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a paraphilia: or guilty ruminations in the presence or major depressive disorder).	The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possession, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder); stereotypies, as in stereotypic movement disorder; ritualized eating behavior, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).
The disturbance is not due to the direct physiological effects of a substance (e.g., drug of abuse, a medication) or a general medical condition.	SAME
Specify if: With poor insight: If, for most of the time during the current episode, the person does not recognize that the obsessions and compulsions are excessive or unreasonable.	*Specify* if: With good or fair insight: The individual recognizes that obsessive-compulsive beliefs are definitely or probably not true or that they may or may not be true. With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true. With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true. *Specify* if: Tic related: The individual has a current or past history of a tic disorder.

I. DSM-IV & DSM-V Criteria for hypomania

J. DSM-V Diagnostic Criteria for borderline personality disorder

Diagnostic criteria of borderline personality disorder*

A pervasive pattern of instability of interpersonal relationships, self-image and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by 5 (or more) of the following:

1. Frantic efforts to avoid real or imagined abandonment. Note: Do not include suicidal or self-mutilating behaviour covered in criterion 5.
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least 2 areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). Note: Do not include suicidal or self-mutilating behaviour covered in criterion 5.
5. Recurrent suicidal behaviour, gestures or threats, or self-mutilating behaviour.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

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k. DSM-IV and DSM-V criteria for Bipolar Disorder

DSM-IV Disorder	DSM-IV Criteria	DSM-5 Disorder	DSM-5 Criteria
Disorder Class	Mood Disorders	Disorder Class	Bipolar and Related Disorders
Bipolar Disorder	DSM-IV specified 6 "types" of bipolar I disorder: • Bipolar I disorder, single manic episode • Bipolar I disorder, most recent episode hypomanic • Bipolar I disorder, most recent episode manic • Bipolar I disorder, most recent episode mixed • Bipolar I disorder, most recent episode depressed • Bipolar I disorder, most recent episode unspecified	Bipolar I Disorder	A. Criteria have been met for at least one manic episode (Table 11). The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes (see Table 9). B. The occurrence of the manic and major depressive episode(s) is not better explained by schizoaffective disorder, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder. Note: Major depressive episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder. Note: Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder. *Specify*: With anxious distress With mixed features With rapid cycling With melancholic features With atypical features With mood-congruent psychotic features With mood-incongruent psychotic features With catatonia With peripartum onset With seasonal pattern *Specify*: Remission status if full criteria are not currently met for a manic, hypomanic, or major depressive episode.
Bipolar I Disorder, Single Manic Episode	A. Presence of only one manic episode (see Table 11) and no past major depressive episodes (see Table 9). Note: Recurrence is defined as either a change in polarity from depression or an interval of at least 2 months without manic symptoms. B. The manic episode is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.		Bipolar I episode "types" dropped from criteria tables, but diagnostic procedure still includes noting most recent episode type.

	Specify if: Mixed: if symptoms meet criteria for a mixed episode *Specify* (for current or most recent episode): Severity/psychotic/remission specifiers With catatonic features With postpartum onset		
Bipolar I Disorder, Most Recent Episode Hypomanic	A. Currently (or most recently) in a hypomanic episode. B. There has previously been at least one manic episode or mixed episode. C. The mood symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. D. The mood episodes in Criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified. *Specify*: Longitudinal course specifiers (with and without interepisode recovery) With seasonal pattern (applies only to the pattern of major depressive episodes) With rapid cycling		Bipolar I episode "types" dropped from criteria tables, but diagnostic procedure still includes noting most recent episode type.
Bipolar I Disorder, Most Recent Episode Manic	A. Currently (or most recently) in a manic episode. B. There has previously been at least one major depressive episode, manic episode, or mixed episode. C. The mood episodes in Criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified. *Specify* (for current or most recent episode): Severity/psychotic/remission specifiers With catatonic features With postpartum onset *Specify*: Longitudinal course specifiers (with and without interepisode recovery) With seasonal pattern (applies only to the pattern of major depressive episodes) With rapid cycling		Bipolar I episode "types" dropped from criteria tables, but diagnostic procedure still includes noting most recent episode type.

	Specify: Longitudinal course specifiers (with and without interepisode recovery) With seasonal pattern (applies only to the pattern of major depressive episodes) With rapid cycling		
Bipolar I Disorder, Most Recent Episode Depressed	A. Currently (or most recently) in a major depressive episode. B. There has previously been at least one manic episode or mixed episode. C. The mood episodes in Criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified. *Specify* (for current or most recent episode): Severity/psychotic/remission specifiers Chronic With catatonic features With melancholic features With atypical features With postpartum onset *Specify*: Longitudinal course specifiers (with and without interepisode recovery) With seasonal pattern (applies only to the pattern of major depressive episodes) With rapid cycling		Bipolar I episode "types" dropped from criteria tables, but diagnostic procedure still includes noting most recent episode type.
Bipolar I Disorder, Most Recent Episode Unspecified	A. Criteria, except for duration, are currently (or most recently) met for a manic, a hypomanic, a mixed, or a major depressive episode. B. There has previously been at least one manic episode or mixed episode. C. The mood symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. D. The mood symptoms in Criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified		
	E. The mood symptoms in Criteria A and B are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism). *Specify*: Longitudinal course specifiers (with and without interepisode recovery) With seasonal pattern (applies only to the pattern of major depressive episodes) With rapid cycling		Dropped