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Original Research Article

Use of Antipsychotic as an Augmenting Agent in Patients of Depression & Obsessive-Compulsive Disorder (OCD)

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Abstract

Background: Atypical antipsychotics are increasingly used to augment antidepressants in patients with depression and obsessive-compulsive disorder (OCD). This study evaluated the prescription patterns, off-label use, and adverse drug reactions (ADRs)of atypical antipsychotics.

Methods: A cross-sectional, observational study was conducted at a tertiary care teaching hospital in India from December 2022 to November 2023. Data from 167 outpatients (141 with depression, 26 with OCD) were collected from case notes and interviews. Adherence to WHO prescribing indicators, off-label use, ADRs, and drug interactions were analysed using descriptive statistics and Pearsons's correlation in Jamovi (v2.3).

Results: Selective serotonin reuptake inhibitors (SSRIs), particularly fluoxetine and as an augmenting agent, olanzapine was mostly prescribed (49% in depression, 42.3% in OCD). Polytherapy was universal, with an average of 3.15 drugs per prescription. Off-label use occurred in 27.1% of depression and 100% of OCD prescriptions. ADRs, mainly hyperacidity and constipation, affected 9.9% of patients, with no significant association with off-label use (p=0.46). A strong correlation was found between illness duration and augmentation duration (r=0.881).

Conclusion: Atypical antipsychotics are widely used for augmentation, in patients with depression & OCD with significant off-label prescribing. Monitoring adverse drug reactions and drug- drug interactions is essential for safe and effective treatment.

Keywords: Depression, Obsessive-Compulsive Disorder, Atypical Antipsychotics, Prescription Patterns, Off-Label Use.

Introduction

The Roman poet Juvenal told around the end of tenth century that," You should pray for a healthy mind in a healthy body" [1] but the concept of healthy mind is deteriorating day by day. It may be due to lack of access to health care facilities, social media usage, post covid-19 effect and isolation & loneliness among people. Depression is the very common mental health disorder seen worldwide. Approximately 280 million people in the world have depression [2]. The current prevalence of depressive disorders in India is 2.68% [3].

Pharmacotherapies available for the treatment of depression includes tricyclic antidepressants (TCA), monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitor (SSRI) and selective noradrenaline uptake inhibitor (SNRI) [4]. These drugs selectively increase the concentration of mono amine transmitter in the brain [5]. Treatment is often started as pharmacotherapy using a single drug such as a selective serotonin reuptake inhibitor [4]. If a patient fails to respond adequately to the initial antidepressant, then other options available are, 1).by increasing the dose of current therapy 2).by changing to another antidepressant 3).the current regimen can be augmented with another drug [6]. Atypical antipsychotics have recently become a major focus for augmentation of traditional antidepressant therapy [6].

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions and/or compulsions, with an estimated prevalence of 1%–3% [7]. In many patients, OCD runs a chronic course which may worsen without treatment [7]. The first-line treatments recommended for OCD are

pharmacological treatment with selective serotonin reuptake inhibitors (SSRIs) [8]. One of the major challenges in the first-line treatment of OCD with SSRIs is that only 40%–70% of patients have an adequate response; the remaining experience either nonresponse or partial response [9]. Switching over to a different SSRI is recommended for those with nonresponse, while augmentation strategies are generally recommended for people with partial response [8].

Very less studies were done in India to evaluate the treatment of depression & obsessive-compulsive disorder (OCD) patient, which requires antipsychotics as an augmentation & pattern of prescribing antipsychotics. So, a need was felt to study their usage pattern, adverse drug reactions and drug- drug interactions due to atypical antipsychotics in the patients of depression & obsessive-compulsive disorder (OCD).

Material & Methods:

This was an observational, cross-sectional study conducted in the department of psychiatry at a tertiary care teaching hospital, aiming to evaluate the prescribing patterns of antipsychotics used as an augmentation strategy in patients with depression and obsessive-compulsive disorder (OCD). The study population comprised, patients of either sex and all age who were diagnosed with depression or OCD, attending the psychiatry outpatient department, and currently receiving antipsychotic medication as augmentation therapy were included. Patients were excluded if they have psychotic symptoms or were indoor (admitted). After ethics committee approval, a total of 167 eligible patients were included (141 with depression, 26 with OCD) and analysed during the study period. Data were collected using a predesigned Case Record Form (CRF). Sources of data included patients' outpatient case notes, treatment charts, and direct interviews with the patients, with no treatment interventions made by the investigators. The information collected included sociodemographic profile (age, gender, education level, occupation, and marital status), clinical details (primary diagnosis and relevant clinical information), and treatment details for antipsychotics and other prescribed medications (drug name, prescribed dose, route of administration, and frequency). Prescription indicators such as average number of drugs per prescription, percentage of drugs prescribed by their generic names, percentage of drugs prescribed from the World Health Organization (WHO) Essential Medicines List, and use of antibiotics and injectable formulations alongside psychotropic medication were also collected. Adverse Drug Reactions (ADRs) were documented, and for each ADR, causality, preventability, and severity were assessed. Instances of off-label prescribing of antipsychotics and potential drug-drug interactions were identified and recorded.

Statistical Analysis Data were compiled and managed using Microsoft Excel 2019. Descriptive statistics were used to summarize the data. Frequencies and percentages were calculated for categorical variables (e.g., gender, education, type of drug, ADR categories). Continuous variables (e.g., age, number of drugs per prescription, drug dosage) were expressed as mean ± standard deviation (SD). Correlations between variables were assessed using Pearson's correlation coefficient. All statistical analyses were performed using Jamovi (Version 2.3, 2022). A p-value of < 0.05 was considered statistically significant

Result:

Out of 167 patients analysed, 141(84%) patients were diagnosed with depression and 26 (16%) patients with OCD.

1. Sociodemographic characteristics:

Sociodemographic details are shown in table 1.

Table 1: Sociodemographic characteristics among patients with depression & OCD

Demographic parameter	Patients diagnosed with depression (n=141) (%)	Patients diagnosed with OCD (n=26) (%)
Age (in years)		
1-20	3(2.12)	3(11.53)
21-40	57(40.4)	16(61.5)
41-60	60(42.5)	6(23.07)
≥61	21(14.8)	1(3.84)
Gender		
Male	69(49)	17(65.38)
Female	72(51)	9(34.61)
Education		
Illiterate	22(15.6)	4(15.38)
Primary	44(31.2)	6(23.07)
Secondary	41(29)	3(11.53)
Higher secondary	13(9.21)	4(15.38)

Graduate	21(14.9)	9(34.61)
Occupation		
Homemaker	67(47.5)	4(15.38)
Working	55(39)	16(61.53)
Non-working	19(13.47)	6(23.07)
Marital status		
Married	87(61.7)	13(50)
Widow/widower	20(14.18)	3(11.53)
Divorced/separated	12(8.51)	9(34.61)
Single	22(15.6)	15(57.6)
Family history of psychiatric illness		
Present	22(15.6)	2(7.69)
Absent	119(84.4)	24(92.3)

2. Prescription Pattern of Antidepressants and Augmenting Atypical Antipsychotics in Depression and OCD

As shown in table 2, antidepressants prescribed were SSRIs, SNRI, serotonin receptor antagonist, atypical antidepressants, and tricyclic antidepressant (TCAs). SSRIs most commonly prescribed were fluoxetine followed by escitalopram and sertraline in both depression & OCD. Augmenting agent most commonly prescribed was olanzapine, an atypical antipsychotic.

Table 2: Prescription pattern of antidepressants & atypical antipsychotic among patients with depression & OCD

Antidepressant Class	**Antidepressant drugs**	**Number of patients with depression N=141**	**Number of patients with OCD N=26**
1.SSRI	Fluoxetine	79	20
	Escitalopram	47	4
	Sertraline	12	2
	Paroxetine	1	NIL
2.SNRI	Desvenlafaxine	1	NIL
3.Serotonin receptor antagonist	Mirtazapine	15	NIL
4.Atypical Antidepressants	Bupropion	1	NIL
5.Tricyclic antidepressant (TCAs)	Amitriptyline	1	NIL
	Clomipramine	1	4
Augmenting agent	**Atypical Antipsychotics**	**N=141(%)**	**N=26(%)**
	Olanzapine	70 (49)	11(42)
	Quetiapine	48(34)	1(3.84)
	Aripiprazole	15 (10.6)	11(42)
	Risperidone	6 (4.25)	3(11.5)
	Amisulpride	2(1.41)	NIL

3. Combinations of antipsychotic plus antidepressants used in patients with depression & OCD: Most prescribed combination of antipsychotic & antidepressants among patients with depression & OCD is Olanzapine+ Fluoxetine.

Table 3: Combinations of antipsychotic plus antidepressants used in patients with depression & OCD

Combination	**Number of patients(n=141)**	**Number of patients(n=26)**
Olanzapine+ Fluoxetine	44	7
Quetiapine+ Escitalopram	21	1
Quetiapine+ Fluoxetine	18	NIL
Olanzapine+ Escitalopram	11	1
Aripiprazole+ Fluoxetine	8	7

4. Off-label drug Use in depression & OCD: Off label drug use is shown in table 4.

Table 4: Off label drug use

Category of off label drug use	Name of drugs	Number of off label prescription in depression (N=141)	Number of off label prescription in OCD (N=26)
Off label indication	Risperidone	6	3
	Olanzapine	19	11
	Amisulpride	2	NIL
	Escitalopram	NIL	4
	Aripiprazole	NIL	11
Off label dosage	Quetiapine	48	NIL
Off label route	Amisulpride	2	NIL
Off label dose	Escitalopram	1	NIL

5. General prescription pattern of drugs in study population: all the patients were receiving polytherapy for depression & OCD. (Table-5).

Table 5: General prescription pattern of drugs in study population

No. of drugs per prescription	n=167	%
One	0	0
Two	10	5.98
Three	127	76.04
Four	24	14.37
five	6	3.59

6. Analysis of WHO prescribing indicators: Out of 167 prescriptions, average number of drugs per prescription was 3.15. None of the patients were prescribed antibiotics and injectable drugs. Of all the drugs, 99% were prescribed by their generic name and 89% of prescribed drugs were from WHO list of essential medicine 2023(Table 6).

Table 6. WHO prescription indicators for drug utilization study

WHO prescribing indicators	Finding
Average number of drugs per prescription (n)	3.15
Percentage of drugs prescribed by generic name	99%
Percentage of drugs prescribed from WHO essential drug list (n)	89%
Total patients receiving antibiotics	0
Total patients receiving injections	0

7. Reported suspected ADR: Out of 167 patients, 9.92 % patients (n=14) developed ADRs. The most common adverse drug reactions noted were hyperacidity (n=8) and constipation (n=6). All ADR were possible according to WHO causality assessment scale, mild in severity according to Hartwing & Siegel scale and preventable according to Modified Schumock & Thornton scale. Among total of 14 ADR reported 10 were among the persons in whom off label drugs was used. Increase in off label use does not cause statistically significant increase in ADR (Chi square P value=0.46).

8. Correlation between duration of psychiatric illness & duration of augmentation: A positive and significant correlation was observed between duration of psychiatric treatment & duration of augmentation (Pearson's correlation coefficient r= 0.881). Scatter plot graphs of the same was plotted for visualization of correlation (Figure 1). Mean time required for antipsychotic augmentation was 2.09 years.

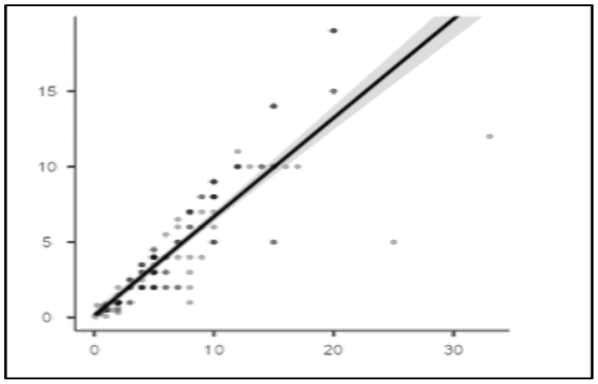

Figure 1: Correlation between duration of psychiatric illness & duration of augmentation

9. Drug-Drug Interaction: Out of 167 cases, there were mainly three potential drug interactions, potential for increase in sedation, potential for QTc prolongation and potential for increase in drug level.

10. Drugs given according national essential medicine list (NLEM) and WHO list of essential medicine: Out of 23 drugs prescribed, 10 (43.47%) drugs including sertraline, paroxetine, desvenlafaxine, mirtazapine, Bupropion, aripiprazole, amisulpride, lorazepam, alprazolam and famotidine do not belong to NLEM & WHO list of essential medicines. Whereas 7 (30.43%) drugs belong to both including fluoxetine, clomipramine, amitriptyline, risperidone, propranolol, omeprazole and syrup lactulose.

Discussion

The observational, cross-sectional study including 141 patients diagnosed with depression & 26 patients with obsessive-compulsive disorder (OCD) requiring antipsychotic augmentation was carried out in psychiatry outpatient department from December 2022 to November 2023.

Depression was more prevalent among individuals aged 21–60 years (mean age 43), consistent with Komaram RB et al. [10], Gerhard et al. [11], and Baig-Ward et al. [12], likely due to career and family stressors . Obsessive compulsive disorder (OCD) was more common in the 21–40 years group (61.5%), aligning with Ruscio A. et al. [13], who noted most cases appear between 18–29 years. Females predominated in depression (51%), consistent with WHO (2024) [2] and NMHS (2016) [3], due to hormonal and social factors.

OCD was more seen in male patients in the present study, though Ruscio A. et al. [13] observed higher female prevalence in adulthood. In the present study it was noted that most patients with depression were having primary & secondary education whereas illiterate patients were less, possibly due to poor mental health awareness, thereby seeking less help. In OCD, graduates (34.6%) were more affected, possibly due to academic stress. Most patients with depression were married (61.7%) [14], though NMHS (2016) [3] found higher rates in widowed/divorced individuals.

In OCD, 57.6% were single, likely due to early onset affecting relationships [15]. It was also noted in the present study that 47.5% of depressed patients were homemakers, reflecting psychosocial stress in women whereas OCD was more common in working individuals (61.53%), indicating that the disease causes significant distress, especially among those who are employed. Family history was positive in 15.6% of depression and 7.69% of OCD cases, supporting genetic links [16,17]. A wide range of effective treatments are available for major depressive disorder (MDD). Pharmacological management not only improves mental health but also enhances patients' physical, occupational, and social functioning, leading to greater optimism and quality of life. In our study, the most commonly prescribed antidepressants were selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, escitalopram, sertraline, and paroxetine, which is consistent with findings by Uppula V. et al [18] and study done by Marasine NR et al. [19] reported sertraline as the most frequently prescribed SSRI, followed by escitalopram, fluoxetine, paroxetine, and fluvoxamine.

Among other classes, amitriptyline was commonly prescribed among tricyclic antidepressants (TCAs), venlafaxine among serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine among serotonin receptor antagonists, and bupropion among atypical antidepressants, findings which also align with study done by Marasine NR et al. [19]. SSRIs remain the most preferred antidepressant class due to their efficacy, safety, tolerability, affordability, and once-daily dosing, with fewer side effects and safer profiles compared to TCAs.

In the case of obsessive-compulsive disorder (OCD), fluoxetine was the most commonly prescribed SSRI in our study, followed by escitalopram and clomipramine. These findings reflect established treatment protocols where SSRIs and clomipramine are frontline therapies for OCD due to their proven efficacy in reducing obsessive-compulsive symptoms.

It is estimated that approximately half of patients with major depressive disorder (MDD) do not respond to their initial antidepressant, and among those who do, only half attain full remission [6]. The STAR*D trial highlighted similar outcomes, with only about one-third of patients achieving remission despite multiple treatment steps [20]. These findings suggest the importance of augmentation strategies, wherein medications with different mechanisms—particularly atypical antipsychotics—are added to enhance antidepressant efficacy.

The combination of aripiprazole or quetiapine with SSRIs and SNRIs and a combination of olanzapine and the SSRI fluoxetine have been FDA approved for treatment-resistant major depression (i.e., following an inadequate response to at least two different antidepressants). Additionally, brexpiprazole is FDA-approved as an adjunct medication for major depressive disorder in adults [5]. In our study, total five atypical antipsychotics were prescribed in combination with antidepressants. In our study, the most commonly prescribed atypical antipsychotics in MDD were olanzapine (49.6%), followed by quetiapine (34%), aripiprazole (10.6%), risperidone (4.25%), and amisulpride (1.41%), similar to findings by Dold M. et al [21] and Shelton et al. [22]. Frequently used

combinations included Olanzapine + Fluoxetine (n=44), Quetiapine + Escitalopram (n=21), Quetiapine + Fluoxetine (n=18), and Olanzapine + Escitalopram (n=11) among 141 patients. These combinations reflect global practices reported by Shelton R. et al. [22], Nelson J. et al. [23], Rapaport MH et al. [24], and Keitner G. et al. [25].

The first-line treatments recommended for OCD are pharmacological treatment with selective serotonin reuptake inhibitors (SSRIs). One of the major challenges in the first-line treatment of OCD with SSRIs is that only 40%–70% of patients have an adequate response; the remaining experience either nonresponse or partial response [8]. Atypical antipsychotics are the most commonly used augmenting agent in OCD patients in developing countries [8].

For OCD, the most common atypical antipsychotics were aripiprazole and olanzapine (42.3%), followed by risperidone and quetiapine. These findings are consistent with studies by Pessina et al. [26], Crocq M. [27], Bogetto F. et al. [28], Carey P. et al. [29], McDougle C. et al. [30], and Hollander E. et al. [31].

The most commonly prescribed combination therapies in our OCD group were Olanzapine + Fluoxetine (n=7) and Aripiprazole + Fluoxetine (n=7), followed by Olanzapine + Fluoxetine + Clomipramine (n=3). Systematic reviews and meta-analysis by Veale D. et al [32]. and Dold M. et al. [33] suggest that antipsychotics like risperidone and aripiprazole may be cautiously used as first-line pharmacological augmenting agents for OCD patients who don't respond to SSRIs and CBT(cognitive behavioural therapy). However, these should be used at low doses and monitored after 4 weeks for effectiveness.

The reviews found no evidence supporting the use of quetiapine or olanzapine compared to placebo [33]. Current evidence suggests that among patients augmented with antipsychotics, one in three SSRI-resistant OCD patients will show a response. So, antipsychotics are currently the first-line pharmacological augmenting agents for OCD [8]. However, there is considerable evidence that second generation antipsychotics can increase the chances of adverse events, including sedation, weight gain and gastrointestinal problems. Use of any FDA approved medication for an unapproved indication, population, and dose or by a different dosage form was referred as off-label use. In our study, risperidone, quetiapine, olanzapine, amisulpride and escitalopram was used off-label among patients with depression. Quetiapine is approved by USFDA in extended-release formulation whereas in our study it was given in tablet form so it is off-label by dosage form. Olanzapine was approved only with fluoxetine whereas in our study nineteen (19) patients received olanzapine with SSRI other than fluoxetine which is off-label.

Amisulpride was approved by USFDA for prevention and treatment of post-operative nausea and vomiting in injectable form whereas in our study it was used in tablet form. Risperidone was approved only for schizophrenia & mania not for depression. In one patient with depression, escitalopram was given in higher dose than FDA approved dose. Whereas in OCD, aripiprazole, risperidone, quetiapine, olanzapine and escitalopram was used off-label as they are not approved by FDA till date in treatment of OCD.

In our study, the average number of drugs per prescription was 3.15, indicating polytherapy was common and no antimicrobials were prescribed which is similar to the study done by Uppula et al. [18]. This exceeds WHO recommendations, highlighting the need to reduce polypharmacy to avoid drug interactions and costs. Notably, 99% of drugs were prescribed by generic name, possibly due to greater awareness in our settings, whereas it was 41.4% in the study done by Uppula et al. [18].

Among 141 patients, 14 adverse drug reactions (ADRs)—mainly constipation and hyperacidity—were observed. All were classified as “probable” by WHO causality scale and of mild severity as per the Hartwig & Siegel scale. Preventability assessment showed all were definitely preventable. Among 14 ADRs, 10 were among the persons in whom off-label drugs were prescribed. However clinically significant association is not found among these two variables. (Chi square p-0.46).

There was a strong positive correlation between the duration of psychiatric treatment and augmentation with atypical antipsychotics, suggesting chronic illness among these patients. The mean time to augmentation was 2.09 years, compared to 98.8 days in study done by Gerhard et al. [11].

In 167 patients, three key types of potential drug interactions were identified:

1. Potential for increased sedation from combining antipsychotics and benzodiazepines;
2. Potential for QTc prolongation from combining SSRIs with certain antipsychotics;
3. Potential for Elevated drug levels due to SSRI-induced CYP enzyme inhibition.

Regarding essential medicines, 43.47% of drugs prescribed (e.g., sertraline, paroxetine, mirtazapine, bupropion, aripiprazole) were not on the WHO or NLEM lists. Some drugs (e.g., escitalopram, quetiapine, and diazepam) appeared on one list but not both, reflecting differences in regional and local morbidity patterns [34].

Conclusion

This study provides insights into the prescription patterns of antidepressants and atypical antipsychotics in patients with depression and OCD. Key findings include a high prevalence of polytherapy, the predominant use of SSRIs and atypical antipsychotics as an augmenting agents and notable off-label drug use among depression and OCD patients. Despite a significant number of off-label prescriptions, adverse drug reactions were relatively low and not significantly impacted by off-label use. The study emphasizes the importance of monitoring drug interactions and adherence to essential medicine lists to ensure safe and effective treatment.

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