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**AN OBSERVATIONAL COMPARATIVE STUDY OF WEIGHT GAIN AND SIALORRHEA
IN PATIENTS TAKING TYPICAL AND ATYPICAL ANTIPSYCHOTICS**

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ABSTRACT

The prevalence of clinically relevant weight gain and obesity has been reported to be four times higher in patients receiving typical or atypical antipsychotic drugs than in general population. Apart from weight gain atypical antipsychotics also cause sialorrhea which can be distressing to psychiatric patients leading to non-adherence to treatment. The present study included 277 patients attending a private psychiatric clinic and counseling centre. Patients were divided based on the use of atypical antipsychotics and combination of both typical and atypical antipsychotics. Details about drug characteristics like number of antipsychotics prescribed, use of anticholinergics, previous history and present occurrence of sialorrhea and weight gain were recorded from patient case sheets and using Simpson Angus Scale. 209 (75.5 %) patients were prescribed with atypical antipsychotics and 68 (24.5 %) patients were prescribed with combination of atypical and typical antipsychotics. Of 209 patients on atypical antipsychotics, 62 patients were on atypical mono therapy among which risperidone was most prescribed 15 (24 %) and least prescribed was clozapine 5 (8 %) and levosulpride 1 (2 %). The overall occurrence of sialorrhea is observed more in patients taking combination therapy. The overall occurrence of weight gain with atypical group and combination group is found to be (64 %) and (55 %) respectively. Patient treated with combination therapy had significant social habits compared to atypical therapy. Clozapine was the least prescribed drug. The overall occurrence of sialorrhea is observed more in patients taking combination therapy compared to patients on atypical therapy.

Key words: Weight gain, sialorrhea, antipsychotics, and combination therapy

INTRODUCTION

Weight gain and sialorrhea are the most concerned side effects of second generation antipsychotics or atypical antipsychotics which are considered as the cornerstone for

the treatment of psychotic diseases like schizophrenia, schizoaffective disorders, bipolar disorder. The use of typical or first generation antipsychotics is associated with side effects like Extrapyramidal side effects which enhanced the use of atypical antipsychotics. Atypical antipsychotics like clozapine, olanzapine, risperidone, quetiapine, are considered to be as effective as typical antipsychotics with fewer extrapyramidal side effects [1]. The four dopamine pathways are involved in the pathophysiology of schizophrenia which is mostly treated with antipsychotics. Typical antipsychotics mainly act by tightly binding to the D2 receptor and blocking its action effectively. They can block H1 (histamine), M1 (muscarinic) and $\alpha 1$ (alpha) receptors. Atypical antipsychotics are those which loosely bind with D2 receptor as the affinity of atypical antipsychotic for D2 receptor is less. They show high affinity for 5HT2A, 5HT1A receptors like Clozapine and Ziprasidone. In addition to this, atypical antipsychotic or second generation antipsychotics have $\alpha 1$, H1, 5-HT2C and M1 antagonist activity [2]. The occurrence of weight gain with antipsychotics is linked to their actions at serotonin 5-HT2A and 5-HT2C, dopamine D2 and D3, histamine H1 and muscarinic M3 receptors. The direct effects of the medications on leptin, adiponectin and ghrelin levels have been associated with weight gain. On the other

hand, effects of antipsychotics on lipid and glucose metabolism are also identified to effect weight gain and adiposity, leading to insulin resistance and hyperlipidaemia condition [3]. Sialorrhea, also known as drooling or ptyalis is a debilitating symptom which occurs when there is excess saliva in the mouth beyond the lip margin. In general the major salivary glands include parotid, submandibular, and sublingual glands the largest being the parotid gland. Salivary secretion is regulated via a reflex arch which has various influences. The afferent branch consists of chemoreceptors in taste buds and mechanoreceptors in the periodontal ligament. Afferent innervations of cranial nerves V, VII, IX and X also play a role by carrying impulses to salivary nuclei in the medulla oblongata. Efferent influences are mainly parasympathetic via cranial nerve VII which control the submandibular, sublingual, and other minor glands, and CN IX which influences the parotid gland [4]. There are two different mechanisms for sialorrhea. 1) Reduced swallowing frequency 2) Increased saliva production [5]. Sialorrhea due to reduced swallowing frequency is caused by neurological diseases, such as Parkinson's disease or cerebral palsy and may also be caused by drugs particularly sedatives. Drugs eliciting extrapyramidal symptoms, mainly antipsychotic agents, may also cause a

reduced swallowing frequency because of rigidity of the throat muscles. The antipsychotic drugs may cause an increase in saliva production. The mechanism behind this is not fully understood but may be related to a 2-adrenergic receptor blockade which leads to hyper salivation. For clozapine, the stronger affinity for the muscarinic subtype of receptors M4 (agonistic) than M3 (antagonistic), this leads to hyper salivation. Furthermore, there is also compromised swallowing frequency due to clozapine induced sedation. Finally, there may be a genetic predisposition for clozapine-induced sialorrhea. Thus weight gain and sialorrhea are to be identified and treated in earlier to avoid no adherence towards treatment.

MATERIALS AND METHODS

A six month, observational comparative study was carried out at a private psychiatric clinic and Counseling Centre. A total of 277 patients were included who fulfilled the inclusion criteria of study. Prior to study initiation, approval was obtained from the institutional ethical committee. Patients of age 10 - 90 years prescribed with both typical and atypical antipsychotics were included in the study. All the necessary details such as chief complaints, diagnosis, co morbidities, social history, family history and other information was obtained from clinical records and by interacting with patients

using data collection form. Patients were divided based on the use of atypical antipsychotics and combination of both typical and atypical antipsychotics. Details regarding drug characteristics like number of antipsychotics prescribed, use of anticholinergics, and dosage form of drug prescribed were recorded. The history and present occurrence of side effects like sialorrhea and weight gain was recorded by interacting with patients and from their case sheets. Statistics like percentages, means and standard deviations (SD) were calculated for all possible variables. 95 % Confidence Intervals was used to gain upper and lower limit around sample mean.

RESULTS

During the study period, a total of 277 psychiatric patients visiting out-patient department were identified. Male patients (57 %) were found to be more compared to female (43 %). Of 277 patients, 209 (75.5 %) patients with mean age of 35.05 (± 13.34) were prescribed with atypical antipsychotics wherein male patients were 117 (55 %) followed by 92 (44 %) female patients. 68 (24.5 %) patients with mean age of 33.11 (± 13.53) were prescribed with combination of atypical and typical antipsychotics. Among these, 40 (58 %) were male and 28 (42 %) were female patients. Out of 209 patients on atypical antipsychotics, 62 patients were on atypical mono therapy among which risperidone 15

(24 %) was prescribed in higher number of patients followed by olanzapine 13 (21 %), amisulpride 13 (21 %), quetiapine 8 (13 %), aripiprazole 7 (11 %), clozapine 5 (8 %) and levosulpride 1 (2 %). The mean age of patients taking atypical monotherapy was found to be 34.90 (\pm 14.10), dual therapy was observed to be 35.84 (\pm 13.4) and mean age of patients on polytherapy was 32.07 (\pm 11.18) **Table 1, 2 and Figure 1.**

Development of weight gain and sialorrhea in patients taking atypical monotherapy:

Patients prescribed with atypical monotherapy also experienced side effects like weight gain and sialorrhea which were listed out in **Table 3.** Most of the side effects were observed in patients taking clozapine and olanzapine.

On comparing the weight gain and sialorrhea experienced by patients taking atypical monotherapy to that of patients on atypical dual therapy, we observed no remarkable difference in weight gain. But occurrence of sialorrhea was observed to be high with dual atypical therapy 53 %. In our study, patients on atypical polytherapy were found to be suffering more from weight gain 82 % and sialorrhea 62 % patients in comparison to that of patients on mono and dual therapy. The weight gain 82 % and sialorrhea 64 % were more with atypical polytherapy than in patients on polytherapy with combination of typical and atypical antipsychotics. **Table 4** depicts the overall comparison of weight gain and sialorrhea observed in both treatment groups.

Table 1: Distribution of Patients Based on Demographics

S. No	Demographics	Atypical	Combination
	<i>Diagnosis</i>	%	%
1.	Schizophrenia	66	43
2.	Schizoaffective Disorder	20	29
3.	Bipolar Disorder	6	22
4.	Others	8	6
	<i>Age</i>	%	%
5.	\leq 18	4	7
6.	19 – 40	68	73
	<i>Area</i>	%	%
7.	Urban	33	53
8.	Rural	67	47
	<i>Social habits</i>	%	%
9.	Smoking	33	23
10.	Alcohol	36	16
11.	Both	30	60
	<i>Marital status</i>	%	%
12.	Married	44	38
13.	Unmarried	36	43
14.	Separated	16	16
14.	Widowed	4	3
	<i>(+) Family history</i>	%	%
15.	Male	68	62
16.	Female	32	38

Table 2: Prescription Patterns of Antipsychotics

S. No.	Type of therapy	Number	%
<i>Atypical(209)</i>			
1.	Mono	62	30
2.	Dual	119	57
3.	Poly	28	13
<i>Combination (68)</i>			
1.	Mono	0	0
2.	Dual	25	37
3.	Poly	43	63
Total		277	

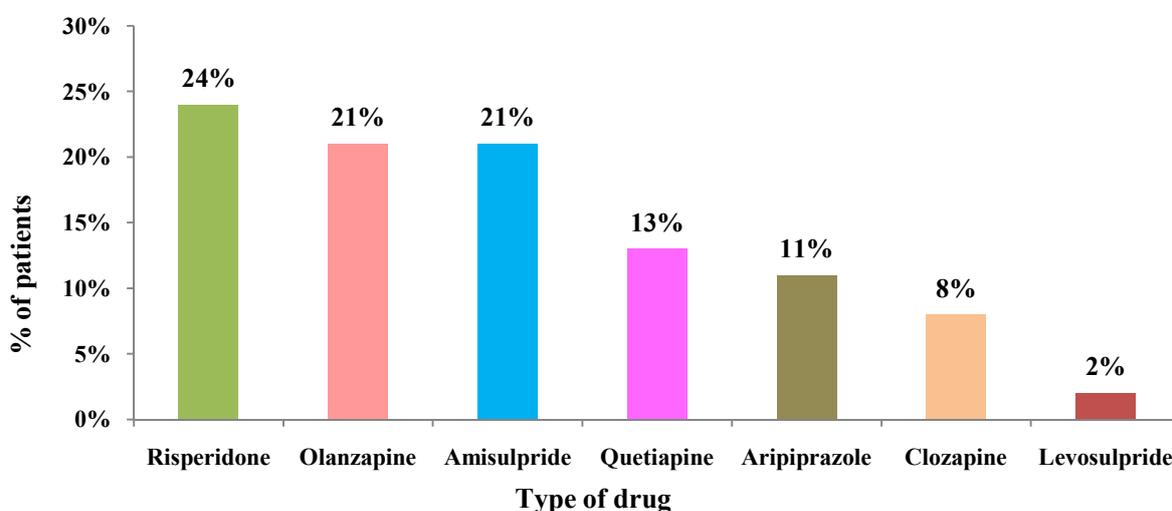


Figure 1: Distribution of Patients on Atypical Mono Therapy Based on Drug Prescribed

Table 3: Development of Weight Gain and Sialorrhea in Patients Taking Atypical Monotherapy

S. No.	Drug	Weight gain (%) n=34	Sialorrhea (%) n=15
1.	Amisulpride	14	20
2.	Aripiprazole	9	7
3.	Clozapine	12	20
4.	Levosulpride	0	0
5.	Olanzapine	29	33
6.	Quetiapine	17	7
7.	Risperidone	18	13

Table 4: Overall Comparisons of Weight Gain and Sialorrhea among Patients on Atypical and Combination Treatment Group

S. No.	Side effect	Atypical (%)	Combination (%)
1.	Weight gain	135 (64 %)	38 (55 %)
2.	Sialorrhea	97 (46 %)	34 (50 %)
Patients		n = 209	n = 68

DISCUSSION: Although new generation or atypical antipsychotics are increasingly replacing conventional antipsychotics like chlorpromazine and haloperidol in some countries, many issues about these compounds need to be clarified [6]. In our study male patients were more and total of 84 (57 %) were male receiving polytherapy in atypical treatment group and 40 (59 %) were among polytherapy in combination treatment group. The mean age of the patients in atypical treatment group and in combination treatment group was 35.05 (± 13.34 ; 95 % CI: 33.2 to 36.9) and 33.11 (± 13.53 ; 95 % CI: 31.3 to 34.9). Most of the patients in our study were suffering from schizophrenia followed by schizoaffective disorder. The most commonly used atypical antipsychotic as monotherapy in our study was risperidone 15 (24 %) and least prescribed was clozapine 5 (8 %). The most commonly used typical antipsychotic in polytherapy was haloperidol. Around (60 %) patients among atypical treatment group were from rural areas and around (33 %) patients were from urban areas. Occurrence of weight gain and sialorrhea were observed more with olanzapine among patients on atypical monotherapy. The use of anticholinergics in atypical group was observed in 188 (90 %) patients and combination group was 65 (95 %). In consistent to our results study done by [7], who stated that men used

antipsychotic drugs more often than women in our study male patients were more in number. In contrast to our findings, study conducted by [8] found more women patients than male. A total of 84 (57 %) were male receiving polytherapy in atypical treatment group and 40 (59 %) were among polytherapy in combination treatment group, as the women with psychotic disorders have better outcomes, possible reasons could include genetic factors, higher rates of marriage among women, lower rates of substance abuse as stated by [9]. The mean age of the patients in atypical treatment group and in combination treatment group was 35.05 (± 13.34 ; 95 % CI: 33.2 to 36.9) and 33.11 (± 13.53 ; 95 % CI: 31.3 to 34.9) which were found to be similar to the results of [10] where mean age was 35.28 (± 10.35). The mean age of patients on monotherapy was 34.90 (± 14.10 ; 95 % CI: 33 to 36.8) and that of polytherapy was found to be 35.84 (± 13.40 ; CI 95% 34 to 37.7) which were consistent to the results of [11], where mean age was found to be 35.7 (11.2) and 36.9 (10.7) for monotherapy and polytherapy groups respectively. Most of the patients in our study were suffering from schizophrenia followed by schizoaffective disorder. Our findings were similar to the results of [12], where bipolar disorder was observed in (6 %) of the patients on monotherapy and

schizoaffective disorder was observed (24.7 %) of patients. Polytherapy (70 %) in atypical treatment group was possibly used to improve sub optimally controlled symptoms of psychiatric disorder. Our results were found to be similar to results of work done by [13], where monotherapy was observed in (34 %) of patients and (66 %) of patients were on polytherapy. Polytherapy can be due to switching of antipsychotics during its failure to exhibit therapeutic efficacy, switching is done gradually rather than abruptly to avoid symptom exacerbation and other rebound phenomena as stated by [14]. The most commonly used atypical antipsychotic as monotherapy in our study was risperidone 15 (24 %) and least prescribed was clozapine 5 (8 %) which might be due to the repetitive hematological test associated with prescribing of clozapine. The results were almost similar to observations made by [12], risperidone (24 %), and clozapine (6.3 %). The most commonly used typical antipsychotics in polytherapy was haloperidol 48 (71 %), whereas Flupenthixol and Zuclopenthixol accounted for about 20 (29 %) of patients. The clozapine along with conventional antipsychotic was used in around (20.5 %) of patients which was within the range of (18.5 %) to (56 %) stated by [15]. Around (60 %) patients among atypical treatment group were from rural areas and around (33

%) patients were from urban areas. In contrast to our findings, [16], stated, the risk of developing schizophrenia is approximately 2.37 times greater in urban compared with rural settings. This discrepancy might be due to the difference in the degree of urbanicity among our region and their region. This can also be attributed to the superstitious believes of the patient associated with poor literacy rate in rural areas in our region and social stigma regarding the occurrence of psychiatric disorders. This may also be affected by the higher number of consanguineous marriages as stated by [17], that a child of consanguineous parents is at increased risk of common mood disorders and psychoses. Occurrence of weight gain: In our study among the patients treated with atypical monotherapy, 55 % patients gained weight which was mostly observed in patients treated with olanzapine 10 (29 %) followed by risperidone 7 (20 %) and less weight gain was observed with aripiprazole 3 (9 %), which were in line with [8], who stated that the patients on olanzapine and risperidone are significantly more likely to gain weight. The mean age of patients who experienced weight gain on treating with atypical antipsychotics was 35 (± 13.44). The weight gain varies with the type of antipsychotic and individual patient factors [3]. Many patient related factors like sedentary life

style, lack of interest at work and self-grooming can affect the weight gain. Weight gain in patients on polytherapy with atypical agents can be explained by the use of two drugs which synergies the effect of weight gain. The overall occurrence of weight gain with atypical group and combination group was observed to be (64 %) and (55 %) respectively. Among the patients who gained weight with combination therapy, (87 %) patients were on antipsychotics that causes more weight gain like olanzapine or haloperidol. The combination use may highly effects weight gain as both conventional and atypical antipsychotic drugs frequently causes clinically relevant weight gain as stated by [18]. Occurrence of sialorrhea: 62 patients treated with atypical monotherapy, sialorrhea or excessive salivation was mostly observed in patients treated with olanzapine (33 %), followed by clozapine (20 %), which is due to its agonistic effect on the M3 and M4 glandular muscarinic receptors which leads to an increase in salivary secretion through the parasympathetic nervous system, and also due to its antagonism at α 2-adrenergic receptors of the sympathetic nervous system. In our study clozapine alone was used in less number of patients and around (16 %) patients were prescribed with clozapine in combination with other antipsychotics. Our findings were similar to

the results of [19], where hyper salivation was observed in (28.9 %) of patients. The overall occurrence of sialorrhea was not remarkably different between two treatment groups. The use of anticholinergics in atypical treatment group was 188 (90 %) and combination group was 65 (95 %), which was similar to the observations made by [20]. The prophylactic use of anticholinergic drugs may worsen the tardive dyskinesia and may cause other side effects like dry mouth, blurred vision, constipation, whereas in older patients it may lead to severe cognitive impairment. Trihexyphenidyl was used in 49 % and combinations like trihexyphenidyl + procyclidine, trihexyphenidyl + Glycopyrrolate were used in 45 % patients taking atypical treatment alone. Whereas 35 % of patients were on trihexyphenidyl and 57 % were on combinations like trihexyphenidyl + procyclidine, trihexyphenidyl + Glycopyrrolate in combination treatment group. (65 %) patients treated with polytherapy, where atypical antipsychotics were augmented with typical antipsychotics were non-adherent to their medications. On the other hand the (47 %) patients were non-adherent in atypical treatment group which was more due to distress associated with weight gain and hyper salivation. In addition to these factors, polytherapy of antipsychotics also

increases the economic burden on patients affecting the adherence.

CONCLUSION

In our study, prevalence of antipsychotic use was mostly observed in rural patients. Most of the patients had positive family history for psychiatric disorders. Risperidone was observed to be the most commonly prescribed atypical antipsychotics and haloperidol was prescribed more often than other typical antipsychotics. Weight gain was mostly observed in patients treated with olanzapine among monotherapy group and the overall occurrence of weight gain was found to be higher in patients on atypical antipsychotic agents. Sialorrhea was observed more in patients on combination therapy. Both weight gain and sialorrhea were observed more in male patients than female. More than half of the patients were prescribed with prophylactic anticholinergic drugs. Patient treated with combination therapy had significant social habits compared to atypical therapy. Nonadherence was mostly observed in patients suffering from weight gain and sialorrhea.

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