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A Systematic Review of Metformin in Treatment of Anti-Psychotics Induced Weight Gain

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Abstract:-

- ***Background:***

Antipsychotic drugs are used in treatment of psychological and neurological disorders. The major side effect of these drugs is weight gain. Metformin has been evaluated to prevent or reduce weight gain. Our aim of the study is to conduct a systematic review on metformin for the treatment of anti-psychotics induced weight gain.

- ***Main Body of the Abstract:***

The primary objective of this review was to evaluate the safety and efficacy of metformin for the treatment of antipsychotics induced weight gain. A systematic review and meta-analysis were conducted with various articles collected in source of original articles through databases like PubMed, Embase, MEDLINE, BMC psychiatry etc. Articles associated with metformin in weight loss for patients with anti-psychotics induced weight gain were included and articles with other interventions were excluded. As a result of total of 257 articles were screened in total and 33 articles were systemically reviewed andarticles were meta-analysed. The risk of bias assessment was done using Cochrane's Risk of bias assessment tool. Meta-analysis was carried out. The forest plot was made using RevMan Software (Version 5.3; Cochrane Collaboration). The studies assessed the effectiveness of the metformin when compared to the control intervention at several time points. The differences between pre and post measurements were calculated in each arm and differences across treatment and control group was taken as the measure. Heterogeneity was quantified by I^2statistic. A Fixed-effect model was used since no significant heterogeneity was detected among studies ($p>0.05$, $I^2<50\%$).

- ***Conclusion:***

The systematic review and meta-analysis concludes that metformin is highly effective in the treatment of patient with anti-psychotics induced weight gain and safe in long term use up to 6 months as it was able to reduce the weight of patients on metformin ranging from 3 to 5 kgs.

***Keywords*:-** *Metformin, Antipsychotics, Weight Gain.*

I. BACKGROUND

Obesity has become a major public health concern as it is responsible for more than 2.8 million deaths worldwide per year with an increased prevalence of cardiovascular disease, cancer, and type 2 diabetes. Despite the randomized clinical trials showing efficacy for lifestyle modification on weight loss, long-term adherence to diet and exercise remains difficult and people oftentimes require pharmacological therapy to manage body weight and metabolic health.

A significant therapy option for many people with schizophrenia and other forms of psychosis is antipsychotic medication. It was shown that many people on antipsychotic drugs gained up to 20% of their initial body weight. Second-generation antipsychotics, sometimes referred to as atypical antipsychotic drugs, are frequently recommended to people with schizophrenia because they have been demonstrated to lower the likelihood of extrapyramidal symptoms and boost treatment responsiveness. Patients who are identified as having first episode psychosis usually start receiving treatment with atypical antipsychotic drugs. Depending on the medication chosen, rapid weight gain is frequently noticed within the first few months of starting treatment. Weight gain and obesity can exacerbate psychological problems including low self-esteem or a negative self-concept.

Numerous studies advise intervention programs that include nutritional guidance and exercise, but efforts to create long-term successful weight control programs have met with only patchy success. Research has shown that individuals using atypical antipsychotic medicines require a variety of early, successful therapeutic weight management measures. The majority of weight loss therapies for people with schizophrenia that have been studied in the literature involve either food changes, exercise, or both. Since many

trials were constrained by attrition and participant non-adherence to the program, it is unclear which of these strategies is most suitable and successful for managing weight among people using atypical antipsychotic medicines. There are no recognized early intervention programs for psychosis that deal with weight control in this demographic. Despite the fact that some workout regimens have shown positive outcomes, more

The American Diabetes Association recommends metformin (also known as 1,1-dimethyl-biguanide) as the first-line oral glucose-lowering drug for persons with type 2 diabetes, prediabetes, and at least one CVD risk factor (such as hypertension, dyslipidemia, etc.). Metformin improves glycemic control through one or more mechanisms, including decreased hepatic glucose synthesis, increased peripheral insulin sensitivity, and inhibition of gastrointestinal glucose absorption. There aren't many studies demonstrating weight loss in people who aren't diabetic, despite the fact that weight loss is frequently cited as a positive 'side-effect' of metformin. Even non-diabetic patients may benefit from metformin as an anti-obesity treatment, according to some research. It asserts that metformin helps people lose weight through influencing brain-based circuits that control hunger, as well as adipose and gut-derived signals.

➢ *Objectives:*

- *Primary Objective:*

To evaluate the efficacy of metformin in treating patients with antipsychotics induced weight gain.

- *Secondary Objective:*

To evaluate safety of metformin in treating patients with antipsychotics induced weight gain.

II. METHADOLOGY

➢ *Study Design:*

A systematic review protocol was developed and meta-analysis was conducted.

➢ *Sources of Data and Materials:*

The systematic review protocol was developed in reference with Preferred Reporting Items for Systemic Reviews and Meta-analysis guidelines. The source of materials were obtained from published original articles through databases of following PubMed, Science direct, British Medical Council Psychiatry, American Journal of Psychiatry, Embase, MEDLINE, Schizophrenia Psychopharmacology, European Journal of Clinical Pharmacology, Schizophrenia bulletin, Journal of American Medical Association, Canadian Journal of Psychiatry, British Journal of Clinical Pharmacology, Psychopharmacology, Journal of Child and Adolescent Psychopharmacology, International Journal of Pharmaceutical Investigation, Human Psychopharmacology.

➢ *Articles Search Strategy:*

The articles search strategy was done using the keywords: Metformin, Antipsychotics induced weight gain, Weight loss.

➢ *Inclusion and Exclusion Criteria:*

The articles showing the association of metformin in weight loss for patients with antipsychotics induced weight gain were included. Articles of only English language were included in the study. The articles of other interventions in treating patients with antipsychotics induced weight gain were excluded.

III. RESULT

➢ *Study Selection*

After an extensive analysis in through the original databases, 257 articles were screened in total and 103 articles were excluded after the examination of title and abstract. After full text analysis, 154 articles were eligible for analysis. In eligible articles, 62 articles were excluded from the study as they did not use metformin in treatment of anti-psychotic induced weight gain and 59 articles were excluded as they explained metformin action in other physiological conditions except anti-psychotics induced weight gain.

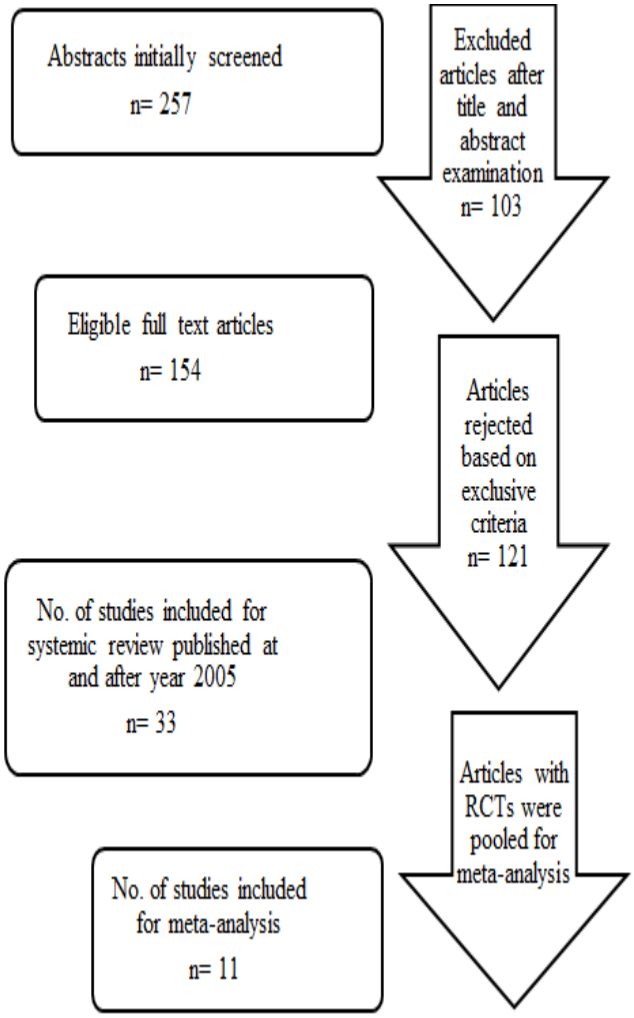

Fig 1 *Study Selection*

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➢ *Assessment of Risk of Bias in Included Studies:*

The risk of bias assessment was done using Cochrane's Risk of bias assessment tool. The risk of bias assessment was done within studies and across studies. The following seven domains were evaluated in each of the study.

- *Random sequence generation [SELECTION BIAS]*
- *Allocation concealment [SELECTION BIAS]*
- *Blinding of participants and personnel [PERFORMANCE BIAS]*
- *Blinding of outcomes assessment [DETECTION BIAS]*
- *Incomplete outcome data [ATTRITION BIAS]*
- *Selective reporting [REPORTING BIAS]*
- *Other bias*

A Review of the author's judgments about each risk of bias item presented as percentages across all included studies is given in the "***Risk of Bias Graph***" [Fig 2]. Review authors' judgments about each risk of bias item for each included study are given in the "***Risk of Bias Summary***" [Fig 3]. Only 10 (91%) of the 11 articles which were included in our study reported randomization details. It was not clear in the remaining one article whether they had used randomization or not. Only six (55%) articles reported details of allocation concealment. Other studies did not provide adequate descriptions of allocation sequencing generation methods or allocation concealment. Around 9 studies (82%) reported the details regarding the blinding of participants and personnel. Except one study, none of the other studies provided the details regarding whether outcome assessment was blinded or not. Selective outcome reporting was unclear in one article and the remaining (91 %) articles had low risk of bias. No other type of bias was found or reported.

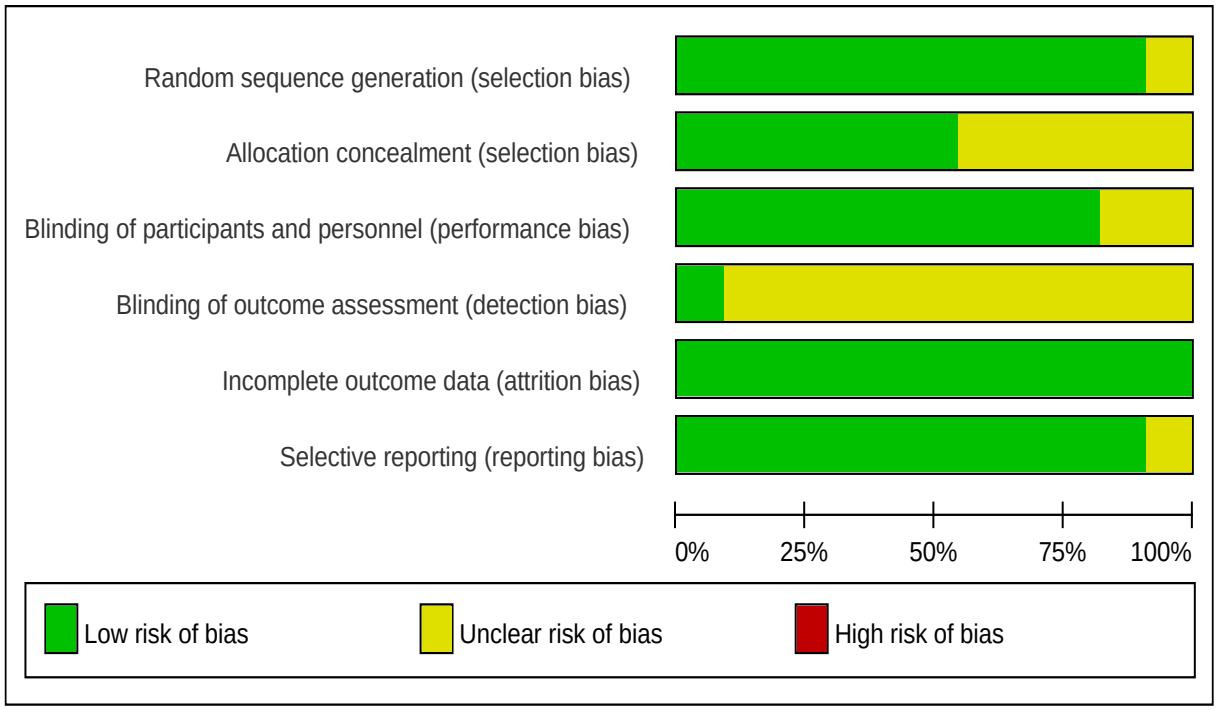

Fig 2 Risk of Bias Graph: Review Authors' Judgments About Each Risk of Bias Item Presented as Percentages Across All Included Studies.

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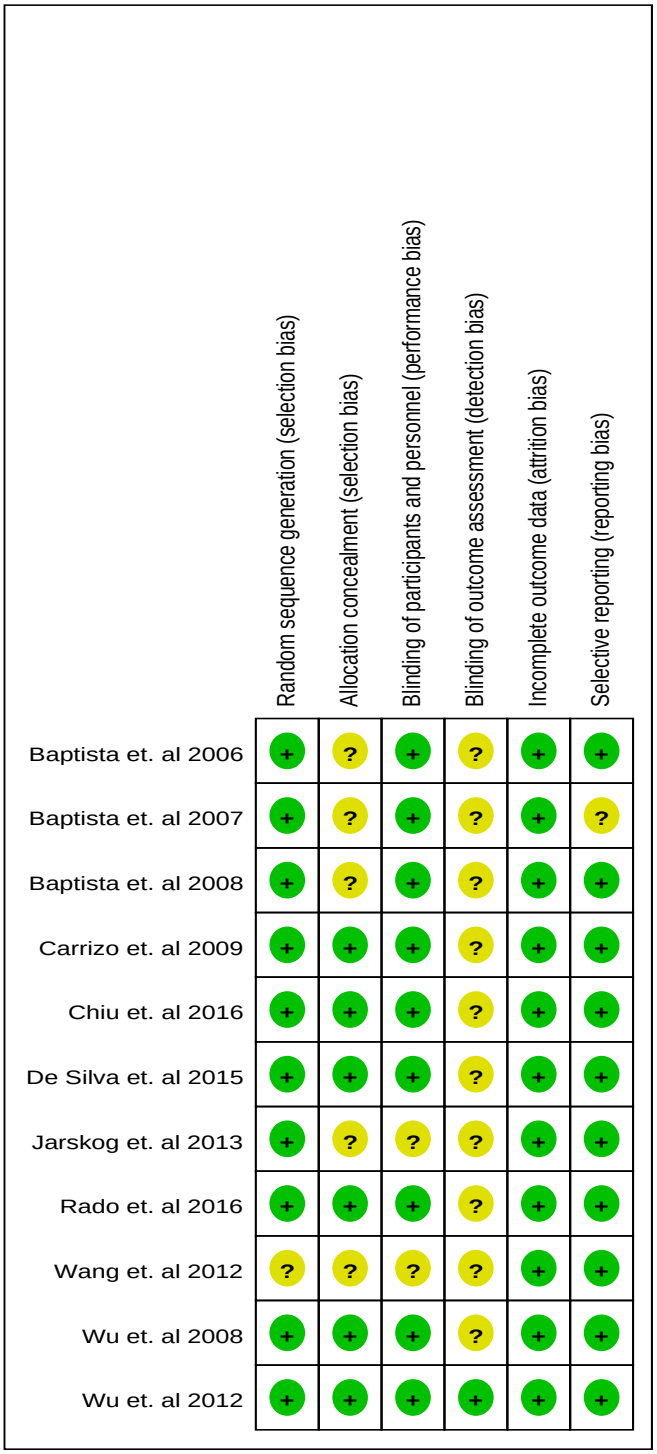

Fig 3 Risk of Bias Summary: Review Authors' Judgments About Each Risk of Bias Item for Each Included Study.

IV. STATISTICAL ANALYSIS

Meta-analysis was carried out and the forest plot was made using RevMan Software (Version 5.3; Cochrane Collaboration). The studies assessed the effectiveness of the metformin when compared to the control intervention at several time points. The timeframe of assessments in the individual studies varied from four weeks to six months. The differences between pre and post measurements were calculated in each arm and then the difference of those differences across treatment and control group was taken as the effect measure. Heterogeneity was quantified by I^2 statistics. A Fixed-effect model was used since no significant heterogeneity was detected among studies ($p>0.05$, $I^2<50\%$). Both the continuous outcomes like weight and BMI obtained from different studies were expressed as differences in means and their corresponding 95% confidence intervals. Pooled effect sizes and the 95% confidence intervals were computed. Forest plot was not constructed to detect publication bias since there was no sufficient number of studies.

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The forest plot of weight and BMI for different time points is given below (Table 1.1 to Table 1.8). The green boxes represent the effect size and the horizontal line represents the 95 % confidence intervals for the individual studies. Details of the study including the name of the lead author and corresponding year of publication is given in the left side of the forest plot. The size of the box represents weight given to each study. The vertical line represents the line of null effect.

Any study line which crosses the line of null effect does not illustrate a statistically significant result. If any study is in the right side of the line of null effect without overlapping it, then that study favors treatment/experimental group. The vertical tip of the black diamond represents the pooled effect estimate obtained from different studies and the width of the diamond represents its confidence interval.

➢ *Tables and Graphs:*

- *Outcome: Weight*

Table 1 Forest Plot of Change in Weight at the First follow up (4th Week)

	Metformin			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
Wu et. al 2008	-1.1	3.8432	32	0.8	3.9611	32	58.2%	-1.90 [-3.81, 0.01]	2008	
Wang et. al 2012	-1.6	5.7105	32	1	5.0567	34	31.3%	-2.60 [-5.21, 0.01]	2012	
De Silva et. al 2015	-0.72	12.8461	34	1.49	13.2024	32	5.4%	-2.21 [-8.50, 4.08]	2015	
Chiu et. al 2016	0	9.3504	19	0.1	10.5532	18	5.1%	-0.10 [-6.54, 6.34]	2016	
Total (95% CI)			**117**			**116**	**100.0%**	**-2.04 [-3.50, -0.58]**		

Heterogeneity: Chi² = 0.55, df = 3 (P = 0.91); I² = 0%

Test for overall effect: Z = 2.75 (P = 0.006)

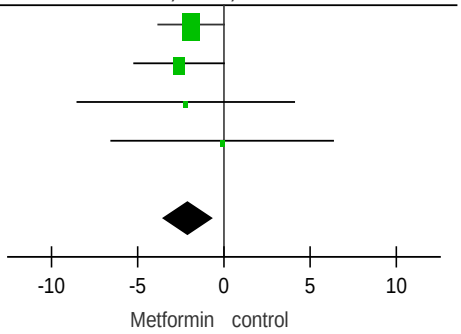

Table 2 Forest Plot of Change in Weight at the Second follow up (Eight/Seven Weeks)

	Metformin			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Baptista et. al 2006	2.2	10.2504	20	2.5	8.5	20	5.8%	-0.30 [-6.14, 5.54]	
Chiu et. al 2016	-0.5	9.1602	19	-0.5	10.4504	18	4.9%	0.00 [-6.35, 6.35]	
De Silva et. al 2015	-0.86	12.9701	34	0.68	13.1341	32	5.0%	-1.54 [-7.84, 4.76]	
Wang et. al 2012	-2.5	5.7105	32	1.5	5.0567	34	28.9%	-4.00 [-6.61, -1.39]	
Wu et. al 2008	-2	3.843	32	1.4	3.8432	32	55.5%	-3.40 [-5.28, -1.52]	
Total (95% CI)			**137**			**136**	**100.0%**	**-3.14 [-4.54, -1.73]**	

Heterogeneity: Chi² = 2.59, df = 4 (P = 0.63); I² = 0%

Test for overall effect: Z = 4.38 (P < 0.0001)

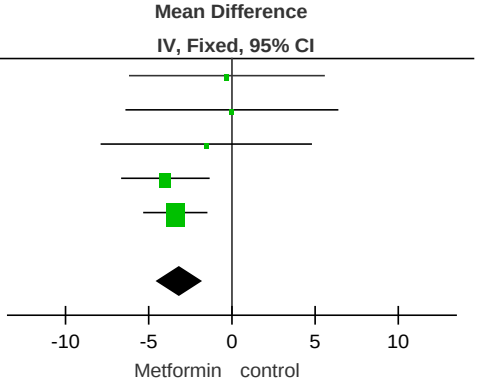

Table 3 Forest Plot of Change in Weight at the Third follow up (12 Weeks)

	Metformin			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Baptista et. al 2007	-1.4	14.6	36	-0.2	17.3139	36	3.2%	-1.20 [-8.60, 6.20]	
Baptista et. al 2008	-2.8	9.3536	13	-1.4	10.6014	15	3.3%	-1.40 [-8.79, 5.99]	
Chiu et. al 2016	-1	9.1602	19	-0.1	10.6057	18	4.3%	-0.90 [-7.30, 5.50]	
De Silva et. al 2015	-1.51	12.721	34	0.73	13.5291	32	4.4%	-2.24 [-8.58, 4.10]	
Jarskog et. al 2013	-4	14.3052	75	-1	20.6727	71	5.3%	-3.00 [-8.80, 2.80]	
Rado et. al 2016	2.03	17.8514	12	5.88	37.3308	13	0.3%	-3.85 [-26.52, 18.82]	
Wang et. al 2012	-3.3	5.7663	32	2.5	5.003	34	26.0%	-5.80 [-8.41, -3.19]	
Wu et. al 2008	-2.8	3.7403	32	2.6	3.7242	32	53.1%	-5.40 [-7.23, -3.57]	
Total (95% CI)			**253**			**251**	**100.0%**	**-4.77 [-6.10, -3.44]**	

Heterogeneity: Chi² = 5.13, df = 7 (P = 0.64); I² = 0%

Test for overall effect: Z = 7.02 (P < 0.00001)

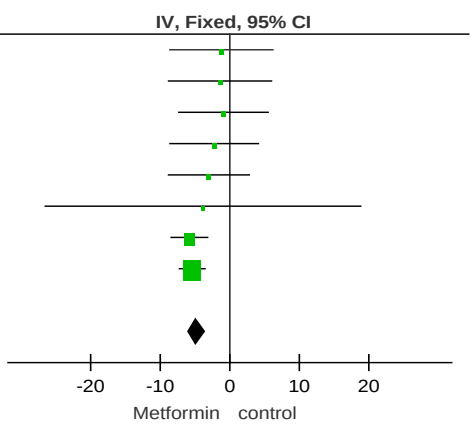

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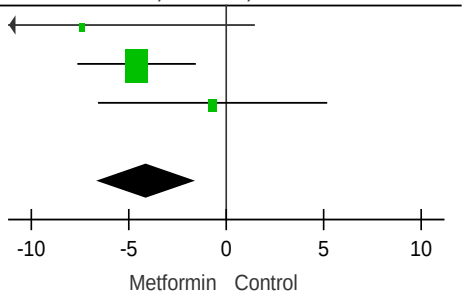
Table 4 Forest Plot of Change in Weight at the Last follow up (Long Term- Six Months/ Fourteen Weeks)

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Carrizo et. al 2009	-13.5	18.1662	24	-6.1	13.9871	30	8.4%	-7.40 [-16.22, 1.42]
Wu et. al 2012	-2.4	5.5653	24	2.2	5.61	30	72.5%	-4.60 [-7.60, -1.60]
Baptista et. al 2006	5.5	10.2504	20	6.2	8.5	20	19.1%	-0.70 [-6.54, 5.14]
Total (95% CI)			**68**			**80**	**100.0%**	**-4.09 [-6.64, -1.54]**

Heterogeneity: Tau² = 0.00; Chi² = 1.95, df = 2 (P = 0.38); I² = 0%

Test for overall effect: Z = 3.14 (P = 0.002)



- *Outcome BMI*

Table 5 Forest Plot of Change in BMI at the First follow up (4th Week)

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Chiu et. al 2016	-0.1	3.5	19	-0.1	3.8	18	1.9%	0.00 [-2.36, 2.36]
De Silva et. al 2015	42.62	11.0912	34	43.3	11.872	32	0.3%	-0.68 [-6.23, 4.87]
Wang et. al 2012	-0.5	1.1136	32	0.3	1.1533	34	35.2%	-0.80 [-1.35, -0.25]
Wu et. al 2008	-0.4	1.0149	32	0.2	0.6083	32	62.6%	-0.60 [-1.01, -0.19]
Total (95% CI)			**117**			**116**	**100.0%**	**-0.66 [-0.98, -0.33]**

Heterogeneity: Chi² = 0.64, df = 3 (P = 0.89); I² = 0%

Test for overall effect: Z = 3.98 (P < 0.0001)

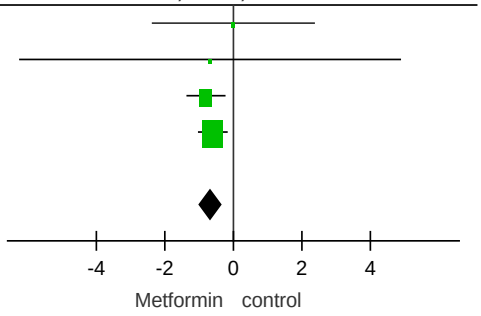


Table 6 Forest Plot of Change in BMI at the Second follow up (Eight/Seven Weeks)

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Chiu et. al 2016	-0.2	3.5	19	-0.3	3.751	18	3.3%	0.10 [-2.24, 2.44]
De Silva et. al 2015	42.48	11.319	34	42.49	11.749	32	0.6%	-0.01 [-5.58, 5.56]
Wang et. al 2012	-0.9	1.179	32	0.5	1.1533	34	57.5%	-1.40 [-1.96, -0.84]
Wu et. al 2008	-0.8	1.4177	32	0.4	1.3892	32	38.6%	-1.20 [-1.89, -0.51]
Total (95% CI)			**117**			**116**	**100.0%**	**-1.26 [-1.69, -0.84]**

Heterogeneity: Chi² = 1.76, df = 3 (P = 0.62); I² = 0%

Test for overall effect: Z = 5.80 (P < 0.00001)

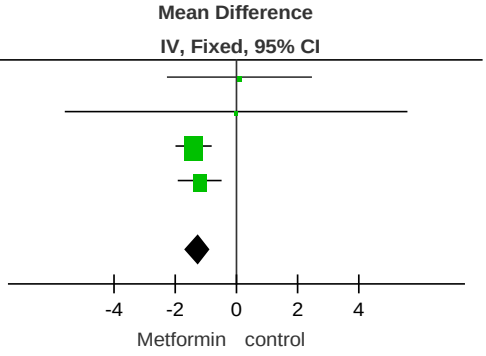


Table 7 Forest Plot of Change in BMI at the Third follow up (12 Weeks)

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Baptista et. al 2007	-0.5	4.9	36	-0.08	5.7	36	1.7%	-0.42 [-2.88, 2.04]
Baptista et. al 2008	-1.1	3.005	13	-0.6	3.9154	15	1.5%	-0.50 [-3.07, 2.07]
Chiu et. al 2016	-0.7	3.5511	19	-0.3	3.751	18	1.8%	-0.40 [-2.76, 1.96]
De Silva et. al 2015	41.83	10.8553	34	42.81	12.4413	32	0.3%	-0.98 [-6.63, 4.67]
Jarskog et. al 2013	-1	5.1	75	-0.3	6.6	71	2.7%	-0.70 [-2.62, 1.22]
Wang et. al 2012	-1.2	1.179	32	0.9	1.2	34	30.2%	-2.10 [-2.67, -1.53]
Wu et. al 2008	-1.1	0.9539	32	0.9	0.6557	32	61.9%	-2.00 [-2.40, -1.60]
Total (95% CI)			**241**			**238**	**100.0%**	**-1.91 [-2.23, -1.60]**

Heterogeneity: Chi² = 6.39, df = 6 (P = 0.38); I² = 6%

Test for overall effect: Z = 11.90 (P < 0.00001)

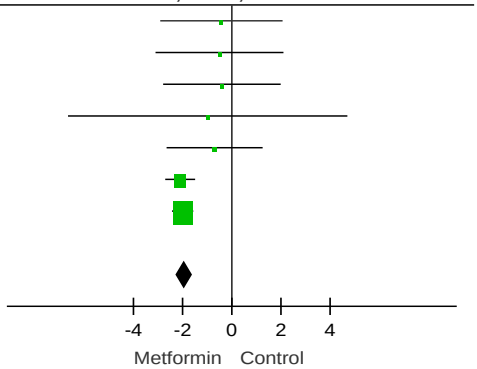


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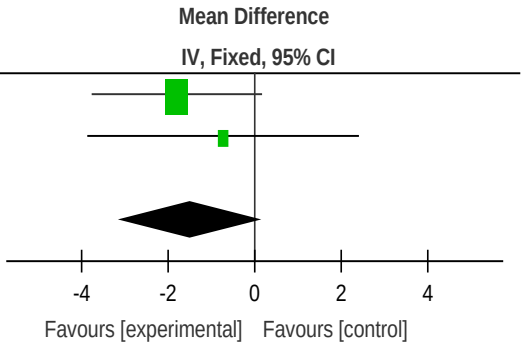
Table 8 Forest Plot of Change in BMI at the Last follow up (Long Term- Six Months/ Fourteen Weeks)

	Metformin			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Baptista et. al 2006	-0.8	2.8	20	1	3.4598	20	71.9%	-1.80 [-3.75, 0.15]
Carrizo et. al 2009	-0.68	5.8643	24	0.05	5.7507	30	28.1%	-0.73 [-3.85, 2.39]
Total (95% CI)			**44**			**50**	**100.0%**	**-1.50 [-3.15, 0.15]**

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%

Test for overall effect: Z = 1.78 (P = 0.08)



V. DISCUSSION

Antipsychotic medications are important therapeutic option for psychiatric and neurological impairments which not only gives a cure but also leads to several side effects like extrapyramidal symptoms, weight gain, amenorrhea, diarrhoea, anxiety, hyperprolactinemia, etc. where weight gain and obesity play a vital part in paving path for other possible co-morbidities. Thus, several clinical studies and review articles claims a solution with pharmacological intervention using metformin for treating patients with antipsychotics induced weight gain.

From the results of meta-analysis conducted among 11 published studies, we were able to prove the significant and statistical difference between the group of patients taking metformin and those on placebo with a weight reduction in patients with antipsychotics induced weight gain. This helps us to conclude that metformin had a reduction of approximately 3-5 kg in all the studies that have been analysed.

After analyzing a wide range of articles, we have assessed that antipsychotic like clozapine, olanzapine, risperidone etc., induce weight gain. Tamara Pringbheim et al. also proved the existence of both metabolic and neurological effects in children who were treated with antipsychotics.

Metformin not only helps to reduce antipsychotics induced weight gain but also has beneficial effects on patients with other co-morbidities like antipsychotics induced amenorrhea, metabolic disorders, Type II Diabetes mellitus.

From the studies concluded from 2016 to 2019, various drugs other than metformin, like aripiprazole, fluvoxamine and topiramate were found to be both safe and effective equivalently with metformin in patients with clozapine induced weight gain.

We were able to deduced a significant result that metformin was effective in reducing both body weight and body mass index at low doses [500mg/day -1000mg/day for a duration of 12 weeks]. Several RCTs that were conducted recently have reported that it is safe to use metformin for a period of 6 months and it have chance of developing metabolic acidosis and vitamin B_{12} deficiency.

Metformin also plays a significant in role introducing new pharmacological targets for obesity and aging associated metabolic disorders.

Metformin is considered to be one of the cheapest anti-diabetic medications which is available in the market with a minimum price of Rs.2 per tablet. After a complete analysis of the selected article, we have assessed that metformin is safe, effective and cheapest method of treatment for anti-psychotic induced weight gain.

VI. CONCLUSION

The systematic review concludes that metformin is highly effective and safe in the treatment of patients with anti-psychotics induced weight gain. We also were able to conclude they not only have an effect on weight gain but also other disorders like anti-psychotics induced amenorrhea and helps in introducing new pharmacological targets for obesity and aging associated metabolic disorders.

It is safe in long term use of metformin up to 6 months with evident results. The safety profile was set as 6 months as prolonged use after this time period may lead to chance of developing vitamin B_{12} deficiency and lactic acidosis.

We recommend metformin dose effective in reducing both body weight and body mass index at low doses of 500mg/day -1000mg/day for a duration of 12 weeks.

The use of metformin in anti-psychotic induced weight gain is efficient and was able to reduce the weight of range 3-5 kgs approximately in all patients with metformin.

From the results and discussion, we give the efficacy and safety of the drug metformin which can be recommended for patients who show evidence of anti-psychotics induced weight gain.

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LIMITATIONS

On basis of level of hierarchy evidences, systemic review and meta-analysis studies are highly prone to bias which alters the outcome of the study. This was overruled by risk of bias assessment for each article that were analysed.

A meta-analysis focuses on relationship between group rate and mean and may not resemble the relation to the most individual valves of exposure and outcome. This may lead to aggression bias or ecologic bias.

The methods of intervention for weight loss other than metformin was not established in our study as we focused only on metformin action on antipsychotics induced weight gain. The outcome parameters used to measure metformin effects were limited to body weight and body mass index as we faced a scarcity of data on other parameters like insulin levels, insulin sensitivity index and prolactin levels etc., falling into our inclusion criteria.

➢ *List of Abbrevations:*

- *RCTs – Randomized Controlled Trails*
- *BMI – Body Mass Index*

REFERENCES

[1]. Siddaway A, Hedges V L, Mathew A W. How to do a systematic review: A best practice guide for conducting and reporting narrative reviews, meta-analysis and meta-syntheses. *Annual Review of Psychology*. 2019 January.

[2]. Steven K Malin, Sageetha R. Kashyap. Effect of metformin on weight loss: potential mechanisms. *Obesity and nutrition*. October 2014; 21:323-329.

[3]. Xiao S. Psychosocial processes influencing weight management among persons newly prescribed atypical antipsychotic medication. *Canada* ,2010 September.

[4]. Mastrigt. S., Addington. J.,and Addington. D. Substance misuse at presentation to an early psychosis program. *Social Psychiatry and Psychiatric Epidemiology*. 2004; 39(1), 69-72.

[5]. Strassnig. M., Brar. J., and Ganguli. R. Body Mass Index and Quality of Life in community dwelling patients with schizophrenia. *Schizophrenia Research*. 2003; 62(1-2), 73-76.

[6]. Weiden. P., and Mackell. J. Differing side effect burden with newer antipsychotics. *European Neuropsychopharmacology*. 1999; 9(1005), 266-266.

[7]. Yerevanian A, Soukas A A. Metformin: Mechanisms in Human Obesity and Weight Loss . 14 march 2019. doi.org/10.1007/s13679-019-00335-3.

[8]. Joao C Hiluy, Bruno P Nazar, Walter S Goncalves, Walmir Coutinho and Jose C Appolinario. Effectiveness of pharmacologic interventions in the management of weight gain in patients with severe mental illness. *Primary care companion CNS Disorder* 2019;21(6): e1-e17

[9]. Siskind D, Friend N, Russell A, McGrath J J, Lim C, Patterson S, Flaws D, Stedman T, *et al*. a protocol for a randomised controlled trial of co-commencement of Metformin as an adjunctive treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia newly commenced on clozapine. *British Medical Journal*-march 5,2018.

[10]. Chih-Chiang Chiu, Mong-Liang Lu, Ming-Chyi Huang, Po-Yu Chen *et al.* Effects of Low Dose Metformin on Metabolic Traits in Clozapine-Treated Schizophrenia Patients: An Exploratory Twelve-Week Randomized, Double-Blind, Placebo-Controlled Study. *PLoS ONE* 11(12), December 14, 2016.

[11]. Paria Hebrani. Double-blind, randomized, clinical trial of metformin as add-on treatment with clozapine in treatment of schizophrenia disorder. *Journal of research medical science* 2015 Apr;20(4):364-71.

[12]. Ulrike Hostalek1, Mike Gwilt, Steven Hildemann. Therapeutic Use of Metformin in Prediabetes and Diabetes Prevention. 10 June 2015 ,75:1071–1094.

[13]. Varuni A de Silva. Metformin for treatment of antipsychotic-induced weight gain in a South Asian population with schizophrenia or schizoaffective disorder: A double blind, randomized, placebo-controlled study. *Journal of Psychopharmacology*, 2015 November 2:1-7.

[14]. Whitney Z, Procyshyn R M, Fredrikson D H, Barr A M. Treatment of clozapine-associated weight gain: a systematic review. *European journal of clinical pharmacology*: 2015 January.

[15]. Prajapati A R. Role of metformin in the management of antipsychotic-induced weight gain. *Progress in Neurology and Psychiatry* 2014 November/December.

[16]. Richard Musil, Michael Obermeier, Paul Russ & Michael Hamerle. Weight gain and antipsychotics: a drug safety review. *Dicle University*. on 2014 November.

[17]. Yuya Mizuno, Takefumi Suzuki, Atsuo Nakagawa, Kazunari Yoshida *et al*. Pharmacological Strategies to Counteract Antipsychotic-Induced Weight Gain and Metabolic Adverse Effects in Schizophrenia: A Systematic Review and Meta-analysis. *Schizophrenia Bulletin Advance*. 2014 March 17.

[18]. Fredrik L Jarskog, Robert M. Hamer, Diane J. Catellier, Dawn D. Stewart *et al*. Metformin for Weight Loss and Metabolic Control in Overweight Outpatients with Schizophrenia and Schizoaffective Disorder. *American Journal of Psychiatry* 2013; 170:1032–1040.

[19]. Generali J A, Cada D J. Metformin: Prevention and Treatment of Antipsychotic-Induced Weight Gain. *Hospital Pharmacy* 2013;48(9):734–735,777.

[20]. Man Wang, Jian-hua Tong, Gang Zhu, Guang-ming Liang *et al*. Metformin for treatment of antipsychotic induced weight gain: A randomised, placebo-controlled study. *Schizophrenia Research* 2012; 138:54-57

[21]. Wu R-R, Jin H, Gao K, Twamley EW *et al*. Metformin for treatment of antipsychotic-induced amenorrhea and weight gain in women with first-episode schizophrenia: a double-blind, randomized, placebo-controlled study. *American Journal of Psychiatry*. 2012; 169(8):813-821.

[22]. C. Seifarth, B. Schehler, H. J. Schneider. Effectiveness of Metformin on Weight Loss in Non-Diabetic Individuals with Obesity. *Exp Clinical Endocrinol Diabetes* 2013; 121: 27–31.

[23]. Tamara Pringsheim, Darren Lam, Heidi Ching and Scott Patten. Metabolic and Neurological Complications of Second-Generation Antipsychotic Use in Children. A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Drug Safety*. 2011; 34 (8): 651-668.

[24]. Yan Ling Chiang, Piyanee Klainin-Yobas, Jeanette Ignacio and Cecilia Mui Lee Chng. The impact of antipsychotic side effects on attitudes towards medication in people with schizophrenia and related disorders. *Journal of Clinical Nursing*, 2011: 2172–2182.

[25]. Lawrence Maayan, Julia Vakhrusheva and Christoph U Correll. Effectiveness of Medications Used to Attenuate Antipsychotic-Related Weight Gain and Metabolic Abnormalities: A Systematic Review and Meta-Analysis. *Neuropsychopharmacology* 2010(35), 1520–1530.

[26]. Edgardo Carrizo, Virginia Fernández, Lisette Connell, Ignacio Sandia *et al.* Extended-release metformin for metabolic control assistance during prolonged clozapine administration: A 14-week, double-blind, parallel group, placebo-controlled study. *Schizophrenia Research* (113) 2009; 19–26.

[27]. Bushe C J, Bradley A J, DoshiS, Karagianis J. Changes in weight and metabolic parameters during treatment with antipsychotics and metformin: do the data inform as to potential guideline development? A systematic review of clinical studies. *International journal of clinical practice* :2009 December 12 ;(63); 1743–1761.

[28]. Lauren Shin, Hallie Bregman, Janis L. Breeze, Nancy Noyes and Jean A. Frazier. Metformin for Weight Control in Paediatric Patients on Atypical Antipsychotic *Medication Journal of child and adolescent psychopharmacology*: Volume 19, Number 3, 2009: 275-279.

[29]. Alvarez-Jimenez, SE Hetrick, C Gonzalez-Blanch, JF Gleeson, and PD McGory. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. Review published: 2008.

[30]. Trino Baptista, Euderruh Uzcátegui , Nairy Rangel , Yamily El Fakih *et al*. Metformin plus sibutramine for olanzapine-associated weight gain and metabolic dysfunction in schizophrenia: A 12-week double-blind, placebo-controlled pilot study. *Psychiatry Research* .2008 June (159) 250–253.

[31]. Wu RR., Zhao JP, Jin H, Shao P *et al*. Lifestyle intervention and metformin for treatment of antipsychotic induced weight gain: a randomized controlled trial. *Journal of American medical association*.2008; 299 (2):185–193.

[32]. Trino Baptista, Nairy Rangel , Virginia Fernández , Edgardo Carrizo *et al* . Metformin as an adjunctive treatment to control body weight and metabolic dysfunction during olanzapine administration: A multicentric, double-blind, placebo-controlled trial. *Schizophrenia Research* 2007 February (93) 99–108.

[33]. David J. Klein, Elizabeth M. Cottingham, Michael Sorter, Bruce A. Barton and John A. Morrison. A Randomized, Double-Blind, Placebo-Controlled Trial of Metformin Treatment of Weight Gain Associated with Initiation of Atypical Antipsychotic Therapy in Children and Adolescents. *American journal of Psychiatry* 2006; 163:2072–2079.

[34]. Trino Baptista, Jessan Martínez, Anny Lacruz, Nairy Rangel, *et al*. Metformin for Prevention of Weight Gain and Insulin Resistance with Olanzapine: A Double-Blind Placebo-Controlled Trial. *Canada Journal of Psychiatry* 2006; 51:192–196.

[35]. Ren-Rong Wu, Jing-Ping Zhao, Zhe-Ning Liu, Jin-Guo Zhai *et al*. Effects of typical and atypical antipsychotics on glucose–insulin homeostasis and lipid metabolism in first-episode schizophrenia. *Psychopharmacology* .2006 (186): 572–578.

[36]. Lucy A. Templeman, Gavin P. Reynolds, Belen Arranz and Luis San. Polymorphisms of the 5-HT2C receptor and leptin genes are associated with antipsychotic drug-induced weight gain in Caucasian subjects with a first-episode psychosis. *Pharmacogenetics and Genomics* 2005, 15:195–200.

[37]. John A. Morrison, Elizabeth M. Cottingham, Bruce A. Barton. Metformin for Weight Loss in Paediatric Patients Taking Psychotropic Drugs. *American Journal of Psychiatry* 2002; 159:655–657.

[38]. Kevin R. Fontaine, Moonseong Heob, Edmund P. Harriganc, Charles L. Shearc *et al*. Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. *Psychiatry Research* 101 (2001): 277-288.

[39]. Kirpichnikov D, McFarlane S I, Sowers J R. Metformin: An Update. *Annals of Internal Medicine journal*. 2002;137: 25-33.

[40]. Amy Lee, John E. Morley. Metformin Decreases Food Consumption and Induces Weight Loss in Subjects with Obesity with Type I1 Non-Insulin-Dependent Diabetes. *OBESITY RESEARCH* Vol. 6 No. 1998 Jan. 1: 47- 53.

[41]. Annick Fontbonne, M. Aline Charles, Irene Juhan-Vague, Jean-Marie Bard *et al*. The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. *Diabetes care* 1996; 19: 920-926.

[42]. Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Nizatidine treatment and its relationship with leptin levels in patients with olanzapine-induced weight gain. *Human Psychopharmacology.* 2003;18(6):457–461.

[43]. Assuncao SS, Ruschel SI, Rosa Lde C *et al*. Weight gain management in patients with schizophrenia during treatment with olanzapine in association with nizatidine. *Rev Bras Psiquiatr*. 2006;28(4):270–276.
[44]. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. *PLoS One*. 2014;9(4): e94112
[45]. Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. *Acta Psychiatrica Scand* 1999: 100: 3-16.
[46]. De Silva, Chathurie Suraweera, Suhashini S. Ratnatunga, Madhubashinee Dayabandara *et al*. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis, *BMC psychiatry* . 2016 (16):341-351.
[47]. Das C, Mendez G, Jagasia S, Labbate LA. Secondgeneration antipsychotic use in schizophrenia and associated weight gain: A critical review and meta-analysis of behavioral and pharmacologic treatments. *Ann Clin Psychiatry*. 2012; 24(3):225-239.
[48]. David B. Allison, Janet L. Mentore, M.S.Ed., Moonseong Heo *et al.* Antipsychotic-Induced Weight Gain: A Comprehensive Research Synthesis. *American Journal of Psychiatry* 1999; (156):1686–1696.
[49]. Fiedorowicz JG, Miller DD, Bishop JR, Calarge CA *et al.* Systematic review and meta-analysis of pharmacological interventions for weight gain from antipsychotics and mood stabilizers. *Curr Psychiatry Rev*. 2012;8(1):25–36.
[50]. Goncalves P, Araujo JR, Martel F. Antipsychotics-induced metabolic alterations: focus on adipose tissue and molecular mechanisms. *Eur Neuropsychopharmacology*. 2015;25(1):1–16.
[51]. Graham KA, Gu H, Lieberman JA, Harp JB, Perkins DO. Double-blind, placebo-controlled investigation of amantadine for weight loss in subjects who gained weight with olanzapine. *The American Journal of Psychiatry*. 2005; 162(9):1744–1746.
[52]. Haneen Abou R, Aburamadan, Sathvik Belagodu Sridhar, Talaat Matar Tadross. Intensive monitoring of adverse drug reactions to antipsychotic medications in the inpatient psychiatry department of a secondary care hospital of UAE. *International journal of Pharmaceutical Investigation* 2018; 8:151-156.
[53]. Jeffrey Rado, Stephanie von Ammon Cavanaugh. A Naturalistic Randomized Placebo-Controlled Trial of Extended-Release Metformin to Prevent Weight Gain Associated with Olanzapine in a US Community-Dwelling Population. *Journal of Clinical Psychopharmacology* 2016;36: 163–168.
[54]. Kristiana I, Sharpe LJ, Catts VS, Lutze-Mann LH *et al*. Antipsychotic drugs upregulate lipogenic gene expression by disrupting intracellular trafficking of lipoprotein-derived cholesterol. *Pharmacogenomics* J. 2010;10(5):396–407.
[55]. Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. *Am J Psychiatry*. 2006;163(12):2072–2079.
[56]. Madhubhashinee Dayabandara, Raveen Hanwella, Suhashini Ratnatunga, Sudarshi Seneviratne *et al*. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. *Neuropsychiatric disease and treatment* 2017;13 :2231-2241.
[57]. Mong-Liang Lu, Tsu-Nai Wang, Tsang-Yaw Lin , Wen-Chuan Shao *et al*. Differential effects of olanzapine and clozapine on plasma levels of adipocytokines and total ghrelin. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015; 58:47–50.
[58]. Poyurovsky M, Fuchs C, Pashinian A, Levi A, Weizman R, Weizman A. Reducing antipsychotic-induced weight gain in schizophrenia: a doubleblind placebo-controlled study of reboxetine-betahistine combination. *Psychopharmacology (Berl)*. 2013;226(3):615–622.
[59]. Prajapati A R. Role of metformin in the management of antipsychotic-induced weight gain. *Progress in Neurology and Psychiatry* November/December 2014.
[60]. Praharaj SK, Jana AK, Goyal N, Sinha VK. Metformin for olanzapine-induced weight gain: A systematic review and meta-analysis. *Br J Clin Pharmacol*. 2011;71(3):377-382.
[61]. Scott Stroup.T, Joseph P. Mc Evoy, Kimberly D. Ring, Robert H. Hamer *et al.* Lieberman; Schizophrenia Trials Network. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). *Am J Psychiatry*. 2011;168(9):947–956.
[62]. G. Paolisso, L. Amato, R.Eccellente, A. Gambardella *et al.* Effect of metformin on food intake in obese subject. *European journal of clinical investigation*. 1998; 28, 441-446.
[63]. Ren-Rong Wu, Jing-Ping Zhao, Hua Jin, Ping Shao, Mao-Sheng Fang *et al*. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain a randomized controlled trial. *Journal of American Medical Association.*2008;299(2): 185-193.
[64]. Stephen M Stahl. How to appease the appetite of psychotropic drugs. *Journal of clinical psychiatry*. 59:10, October 1998:500-501.
[65]. Richard J. Wurtman, Judith J. Wurtman. Brain Serotonin, Carbohydrate-Craving, Obesity and Depression. *Obesity Research*. 1995;3(Suppl4):477S-48OS.