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REVIEW

Metabolic complications of psychotropic medications in psychiatric disorders: Emerging role of *de novo* lipogenesis and therapeutic consideration

Mohammad M Khan, Zaw Ali Khan, Mohsin Ali Khan

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Mohammad M Khan, Laboratory of Translational Neurology and Molecular Psychiatry, Department of Biotechnology, Era's Lucknow Medical College and Hospital, and Faculty of Science, Era University, Lucknow 226003, India

Zaw Ali Khan, Mohsin Ali Khan, Era's Lucknow Medical College and Hospital, Era University, Lucknow 226003, India

Corresponding author: Mohammad M Khan, PhD, Professor, Laboratory of Translational Neurology and Molecular Psychiatry, Department of Biotechnology, Era's Lucknow Medical College and Hospital, Faculty of Science, Era University, Sarfarazganj, Hardoi Road, Lucknow 226003, India. mmkhan0@gmail.com

Abstract

Although significant advances have been made in understanding the pathophysiology of psychiatric disorders (PDs), therapeutic advances have not been very convincing. While psychotropic medications can reduce classical symptoms in patients with PDs, their long-term use has been reported to induce or exaggerate various pre-existing metabolic abnormalities including diabetes, obesity and non-alcoholic fatty liver disease (NAFLD). The mechanism(s) underlying these metabolic abnormalities is not clear; however, lipid/fatty acid accumulation due to enhanced *de novo* lipogenesis (DNL) has been shown to reduce membrane fluidity, increase oxidative stress and inflammation leading to the development of the aforementioned metabolic abnormalities. Intriguingly, emerging evidence suggest that DNL dysregulation and fatty acid accumulation could be the major mechanisms associated with the development of obesity, diabetes and NAFLD after long-term treatment with psychotropic medications in patients with PDs. In support of this, several adjunctive drugs comprising of anti-oxidants and anti-inflammatory agents, that are used in treating PDs in combination with psychotropic medications, have been shown to reduce insulin resistance and development of NAFLD. In conclusion, the above evidence suggests that DNL could be a potential pathological factor associated with various metabolic abnormalities, and a new avenue for translational research and therapeutic drug designing in PDs.

Key Words: Psychotropic medications; Metabolic complications; *De novo* lipogenesis;

Obesity; Diabetes; Non-alcoholic fatty liver disease

Core Tip: Psychotropic medications are the first line of treatment for psychiatric disorders; however, their long-term use has been shown to induce various metabolic abnormalities including diabetes, obesity, and fatty liver disease. Although mechanism(s) underlying these metabolic abnormalities is not clear, lipid/fatty acid accumulation caused by enhanced *de novo* lipogenesis (DNL) could be the primary mediator. In this regard, various anti-inflammatory drugs that are used in combination therapy, have been shown to reduce DNL and the aforementioned metabolic abnormalities in laboratory animals. This suggests that DNL could be a potential pathological and therapeutic target, and a new avenue for translational research in psychiatric disorders.

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INTRODUCTION

Although a great success has been made in understanding the pathophysiology of psychiatric disorders (PDs), therapeutic advances have not been very convincing[1-4]. While psychotropic medications including antipsychotic drugs (APs) and antidepressants (ADs) can reduce classical symptoms in patients with PDs, their long-term use has been reported to induce the development or exacerbate various pre-existing metabolic abnormalities including insulin resistance, adiposity/obesity and non-alcoholic fatty liver disease (NAFLD)[5-8]. Evidence suggests that oxidative stress and inflammation could be the major risk factors associated with various metabolic abnormalities in PDs; however, the underlying mechanisms remain(s) unclear[8-12]. Finding the underlying mechanism(s) could play a crucial role in developing effective therapies/drugs for minimizing the development of various metabolic abnormalities and improving treatment outcome and the quality of life in patients with PDs.

Over the years several mechanisms have been sown to induce oxidative stress and inflammation and associated metabolic abnormalities, they are triggered initially by the accumulation of intracellular fatty acids synthesized *via de novo* pathway/*de novo* lipogenesis (DNL)[12-19]. Although DNL produces both saturated fatty acids (SAFs) and monounsaturated fatty acids (MUFAs), evidence suggest that effect of SAFs on metabolic abnormalities could be detrimental as they increase oxidative stress and inflammation by disrupting calcium homeostasis, endoplasmic reticulum (ER) and mitochondrial function, whereas, MUFAs can induce metabolic abnormalities, specially, insulin resistance even without increasing oxidative stress and inflammation[17-21]. Since both APs and ADs have been shown to induce/deteriorate insulin resistance and other metabolic abnormalities, their effects could be most likely mediated *via* enhanced DNL.

In this review, several emerging evidence are discussed, which suggest that lipid/fatty acid accumulation caused by enhanced DNL could be the primary mechanism associated with the development of obesity, diabetes, and NAFLD during long term treatment with psychotropic medication in patients with PDs. In support of this, outcome of preliminary clinical trial studies and prospects of various adjunctive drugs/anti-inflammatory agents in reducing the development of the aforementioned metabolic abnormalities in patients with schizophrenia and depression are discussed. References cited in this review article were searched using PubMed, Scopus and Google. Only indexed articles published in English within the last five years were included. Articles published in French or German were considered only when necessary. Older articles were considered only when deemed necessary.

OVERVIEW OF PSYCHOTROPIC MEDICATIONS

Psychotropic medications are synthetics drugs/agents used in treating a wide variety of PDs including schizophrenia psychosis, depression, bipolar disorder, mood disorder, anxiety, attention deficit hyperactivity disorder and others[22]. The most common psychotropic medications are APs, ADs, mood stabilizers, and anxiolytics or anti-anxiety drugs. However, in this review we have focused mainly on APs and ADs, their receptor binding profiles and mechanism of action are shown in Table 1.

APs

APs are the first line of treatment for schizophrenia and related psychiatric conditions. They are broadly classified into two categories; first generation or typical APs and second generation or atypical Aps[23,24]. Regarding the mechanism of action, first-generation APs are designed to block dopaminergic neurotransmission, and it has been suggested that their effectiveness is optimum when they block about 72%-75% of the dopamine-2 (D2) receptors in the brain. In addition to D2

Table 1 Commonly used antipsychotic drugs and antidepressants, main mechanism of action and weight gain

Antipsychotic drugs	Main mechanism of action[23-25]	Main mechanism of action[28,29]	Weight gain[8,26,27]	Weight gain[31,32]
Typical APs				
Chloropromazine	Blocks post-synaptic dopamine D2 receptors in the brain		+++	
Haloperidol	Blocks post-synaptic dopamine D2 receptors in the brain		+	
Thiothixene	Blocks post-synaptic dopamine D1, D2, D3, D4 receptors in the brain		+++	
Fluphenazine	Blocks post-synaptic dopamine D1 and D2 receptors in the brain		+	
Atypical APs				
Clozapine	Blocks dopamine D2 and 5HT serotonin receptors in the brain		+++	
Olanzapine	Blocks dopamine D1, D2, D3, D4 receptors, and serotonin 5HT2A, 5HT2C, 5HT3 and 5HT6, the alpha-1 adrenergic receptor		+++	
Quetiapine	Blocks dopamine D2 and serotonin 5HT2A receptors		+++	
Ziprasidone	Blocks dopamine D2 and serotonin 5HT2A receptors		-/+	
Risperidone	Blocks dopamine D2 and serotonin 5HT2A receptors		++	
Aripiprazole	Partially agonizes dopamine D2, 5-HT1A receptors, blocks serotonin 5HT2A receptors		+	
Paliperidone	Blocks dopamine D2 and serotonin 5HT2A receptors		+	
Zotepine	Blocks dopamine D1, D2 and serotonin 5HT2A, 5HT2C, 5HT6 receptors		+++	
Sertindole	Blocks dopamine D2 and serotonin 5HT2A, 5HT2C alpha-1 adrenergic receptor		+	
Amisulpride	Blocks dopamine D2 and D3 receptors		+	
Antidepressants				
SSRIs				
Sertraline		Increase serotonin 5HT level by blocking reuptake at presynaptic terminals		++
Fluoxetine				
Excitalopram				
Trazodone				
Citalopram				
Paroxetine				
SNRIs				
Duloxetine		Block serotonin and norepinephrine reuptake in the synapse, increase postsynaptic receptors' stimulation		++
Venlafaxine				
Levomilnacipran				
Atypical ADs				
Bupropion		Inhibits reuptake of dopamine and norepinephrine at the presynaptic cleft by binding to norepinephrine transporter and dopamine transporter		+

Mirtazapine	Increases release of norepinephrine into the synapse by blocking alpha-2 adrenergic receptors. Also antagonizes 5-HT receptor, increasing norepinephrine and dopamine	++
Viladozone	Enhances the release of serotonin across the brain's serotonergic pathways specifically by inhibiting the serotonin transporter	
Tricyclic ADs		
Imipramine	Increase norepinephrine and serotonin concentration by inhibiting reuptake at the presynaptic neuronal membrane	+++
Nortriptyline		
Amitriptyline		
Doxepin		
MAOIs		
Phenelzine	Increase the levels of norepinephrine, epinephrine, serotonin, and dopamine by blocking reuptake of catecholamines and serotonin at the presynaptic neuronal membrane	++
Isocarboxazie		
Tranylcypromine		

APs: Antipsychotic drugs; ADs: Antidepressants; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin and norepinephrine reuptake inhibitors; MAOIs: Monoamine oxidase inhibitors; 5-HT: 5-hydroxytryptamine.

receptor blocking, first generation APs have been found to also block noradrenergic, cholinergic, and histamine receptors. On the other hand, second-generation APs work by blocking D2 receptors as well as serotonin (5-hydroxytryptamine) receptor. Among the various serotonin receptors, 5-HT2A subtype of serotonin receptor is most commonly involved in the action of second-generation APs[23-25].

Although APs effectively reduce psychotic symptoms but, when used for extended duration, they can induce various adverse effects including sedation or dry mouth, constipation, akathisia, sexual dysfunction, acute dystonia, tardive dyskinesia, myocarditis, agranulocytosis and weight gain. Some adverse effects of APs such as hyperprolactinemia and dyslipidemia may involve long-term risk of medical complications. Although compared to the typical APs, atypical APs have been found to have the lowest propensity to cause extrapyramidal symptoms but they have highest propensity for causing weight gain and metabolic syndrome[8,26,27].

ADs

ADs are used for treating depression and major depressive disorders[22]. Over the years numerous ADs have been developed and approved by Food and Drug Administration for treating children, adults and geriatric patients with depression/major depression and various related conditions[28,29]. ADs are classified into the following groups: Selective serotonin re-uptake inhibitors (SSRIs), selective serotonin and norepinephrine re-uptake inhibitors (SNRIs), tricyclic ADs (TCAs), monoamine oxidase inhibitors and atypical ADs[28,29]. Evidence suggests that overall outcome and tolerance profile is better with the more recent ADs (SSRIs, SNRIs) than with the older agents (TCAs). Receptor binding profiles and mechanisms of action of various ADs are shown in Table 1.

Although ADs can effectively reduce symptoms of depression, their long-term use, like APs, has been shown to induce various side effects including sexual dysfunction, gastrointestinal problems, sleep disturbance, apathy, fatigue/drowsiness, insomnia, tremor, apathy and weight gain[30]. A recent meta-analysis has reported that weight gain was more prevalent in patients who received long-term treatment with TCAs[31,32]. We have discussed later the role of DNL and the mechanism associated with weight gain and other metabolic abnormalities induced by long-term treatment with both APs and ADs.

OVERVIEW OF *DNL*

Lipogenesis is a term used for lipid synthesis from fatty acids obtained either from the diet or synthesized *de novo* from glucose inside the cells. One the other hand, the term DNL is used for lipid synthesis from fatty acids, which are synthesized exclusively by *de novo* pathway from glucose. Excess glucose obtained from the diet or synthesized from intermediary metabolites including citrate, lactate, pyruvate, glutamate, glutamine, and glycerol can be converted into glucose and used in DNL[33-35].

In energy sufficient states or fed state, glucose is converted to pyruvate through glycolysis. Pyruvate then enters mitochondria to metabolize through Krebs cycle (tricarboxylic acid cycle) and produce citrate, which is transported back into the cytosol where it is converted to acetyl-CoA. DNL starts with ATP-dependent carboxylation of acetyl-CoA leading to the production of malonyl-CoA. In the next step, alonyl-CoA and acetyl-CoA are converted into palmitic acid (a C16 SFA) by a multi-subunit enzyme called fatty acid synthase. Palmitic acid is the predominant fatty acid synthesized during DNL. Palmitic acid can be further elongated to yield stearic acid (a C18 SFA) and also undergoes desaturation process by

the enzyme stearoyl-CoA desaturase-1 (SCD-1) to produce palmitoleic acid (C16:1 MUFA). Evidence suggest that SCD-1 can convert stearoyl-CoA to oleoyl-CoA, which is a major source for triacylglycerol (TG) synthesis. Palmitic acid and stearic acid can be further elongated and desaturated to give higher MUFAs including nervonic acid as the terminal product[33-35]. Although under normal physiological conditions DNL is a tightly regulated process, enhanced DNL has been associated with various metabolic diseases[35], which could be a likely scenario in patients with PDs treated with psychotropic medications[12].

PSYCHOTROPIC MEDICATIONS ENHANCE *DNL*

Over the years several studies have shown that membrane lipid/fatty acid abnormalities are strongly associated with cognitive and classical symptoms in patients with PDs[36-39]. Although most of these studies have focused mainly on polyunsaturated fatty acids (PUFAs), little or no attention is given to the role of SAFs and MUFAs, which are supplied mainly by DNL. Evidence suggests that DNL is essential for brain and peripheral tissue development and metabolic homeostasis[40-43]. However; enhanced DNL has been associated with inflammation and various metabolic abnormalities including insulin resistance/diabetes, obesity, and NAFLD[12,13,34,35,44-48]. Since psychotropic medications have been shown to induce or exaggerate these metabolic abnormalities, enhanced DNL could be a major mediator.

Red blood cells (RBCs) membrane fatty acids (SAFs and MUFAs) have been used to measure the extent of DNL in health and disease including PDs[46,49-51]. In schizophrenia, we reported long back that the levels of RBC's SFAs, MUFAs, and PUFAs were significantly elevated in patients with psychosis treated with APs compared to the untreated patients and control subjects (Figure 1 and Table 2)[36]. A number of other studies including those conducted in recent years have also reported similar changes in the levels of SFAs, MUFAs, and PUFAs in the RBC membrane from patients with psychosis after treatment with APs[37-39,42,52,53]. In addition to RBCs fatty acids, plasma free fatty acids and TG levels have also been found to be significantly increased after treatment with APs[54-56]. Changes in membrane fatty acids and TGs seem to be the result of enhanced DNL, and not due to binge eating or other confounders because; they showed strong association with cognitive and clinical symptom scores[37-39,57].

In depression, several studies have reported increase in the RBC's fatty acid contents after treatment with various ADs [58-61]. Evidence suggests that treatment with ADs can also increase plasma as well as hepatic TGs most likely by increasing DNL[62]. Further, changes in various fatty acids and TG levels were strongly associated with clinical symptoms scores in patients with depression[59-62]. Altogether, the above evidence suggests that treatment with both APs and ADs can increase the levels of both SFAs and MUFAs *via* increasing DNL in patients with PDs. This could be a potential risk factor associated with various metabolic abnormalities including insulin resistance/diabetes, obesity and NAFLD induced by long-term treatment with psychotropic medications.

PSYCHOTROPIC MEDICATIONS INDUCE DIABETES

Evidence suggests that under normal physiological condition, insulin regulate both gluconeogenesis and DNL, whereas, insulin resistance stimulates gluconeogenesis and DNL[47,63]. It has been reported in humans that the level of SAFs of DNL in adipose tissue is negatively associated with insulin sensitivity[64]. Thus, elevated SFAs along with MUFAs synthesized *via* DNL could be the major players involved in insulin resistance in patients with PDs.

Although evidence suggest that insulin resistance could be developed from the early stage of the illness in patients with PDs, treatment with psychotropic medications may further deteriorate insulin resistance[65-68]. In drug-naïve patients with early psychosis, Steiner *et al*[69] assessed homeostatic model assessment of insulin resistance (HOMA-IR) and stress hormone levels, and found that insulin resistance and disrupted glucose homeostasis could be illness related and not due to pharmacotherapy, adiposity, or hormonal stress axis activation; although, levels of serum stress hormone may be increased. In another study, Chouinard *et al*[68] studied insulin resistance in patients with first-episode psychosis and suggested that abnormal glucose metabolism could be related to risk for psychosis, independent of disease expression and treatment effects. Pillinger *et al*[70] performed a meta-analysis and noticed elevated HOMA-IR in drug-naive patients with first-episode compared with controls. Thus, while the above evidence suggest that insulin resistance may develop from the early stage of the illness in patients with PDs, recent studies have reported that treatment with APs further deteriorate insulin resistance, which could be aligned with the increase in body weight[71,72].

Likewise, in depression several studies have shown that insulin resistance could be present in a significantly high proportion of patients before the diagnosis of classical symptoms, and it may either remain unchanged or deteriorate further leading to the development of diabetes and obesity after long-term treatment with ADs[65,67,73,74]. Although, there may be some controversies, a recent meta-analysis has reported that risk of insulin resistance is also increased even in children and adolescence after treatment with ADs[75]. Altogether, the above evidence suggests that insulin resistance could be an intrinsic risk factor, which may deteriorate further triggering the development of obesity and NAFLD following treatment with psychotropic medications.

Table 2 Effect of psychotropic medications on the markers of *de novo* lipogenesis, gluconeogenesis and metabolic abnormalities in patients with psychiatric disorders

Parameters	Antipsychotic drugs	Antidepressants
De novo lipogenesis (markers)		
SFAs	Increased[36,39]	Increased[58,61]
MUFAs	Increased[36,39]	Increased[58,61]
PUFAs[1]	Increased[36,39]	Increased[58,61]
Gluconeogenesis (precursors)		
Lactate	Increased[125,126]	Decreased[128]
Citrate	Increased[129]	?
Pyruvate	Increased[129]	Increased[128]
Glutamate	Increased[129,130]	Increased[128]
Metabolic abnormalities		
Blood glucose	Increased[72,121]	Increased[122,131]
IR/insulin level[2]	Increased[55,133]	Increased[65,74,75]
Triglycerides	Increased[8,55,56,72]	Increased[122]
Obesity (BMI)	Increased[8,55,72]	Increased[31,32,122]
Leptin	Increased[57,87]	Increased[132]
Adiponectin	Increased[55,89]	No change[65,134]
Resistin	Increased[55,89]	Reduced[134]
Diabetes	Increased[8,55,72]	Increased[5,65,74,135]
NAFLD	Increased[7,97,123]	Increase[95,96]

[1]Polyunsaturated fatty acids are obtained through the diet, they are not synthesized *via de novo* lipogenesis in the body.
[2]Insulin resistance is a positively and strongly associated with *de novo* lipogenesis.
SFAs: Saturated fatty acids; MUFAs: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids; IR: Insulin resistance; BMI: Body mass index; NAFLD: Non-alcoholic fatty liver disease.

PSYCHOTROPIC MEDICATIONS INCREASE ADIPOSITY/OBESITY

Although patients with PDs may have elevated risk for adipose tissue dysfunction from the early stage of illness, obesity usually develops or become more severe after treatment with psychotropic medication[72,73,76,77]. Adipose tissue is one of the two major sites for DNL under normal conditions, evidence suggests that adipose tissue DNL could be enhanced in patients with PDs[12,55,57,60,61,67]. Although adipocytes can synthesize and store excess lipids/fats without being inflammatory, insulin resistance has been associated with adipocyte hypertrophy and secretion of pro-inflammatory cytokines[78-80]. In addition, hypersensitized adipocytes can released SAFs and MUFAs into circulation, which can lead to the activation and transformation of circulating monocytes into macrophages[81,82]. Intriguingly, several evidence suggest that monocytes could be activated and associated with increased macrophage activation and inflammation in patients with PDs[83,84]. Activated macrophages, in turn, can accumulate SAFs *via* enhanced DNL and secrete various pro-inflammatory cytokines in adipose tissue; some of these cytokines such as tumor necrosis factor (TNF)-α, can activate nearby adipocytes leading to the formation of a paracrine inflammatory loop between macrophages and adipocytes[14,15,81,82]. Evidence suggests that formation of inflammatory loop between adipocytes and macrophages can result in hypersensitization of adipose tissue leading to irreversible increase in body weight and insulin resistance[81,82].

Adipocyte-macrophage inflammatory cascade, involving activated monocytes, could be the primary mediator of adipose tissue abnormalities induced by long-term treatment with psychotropic medications in patients with PDs[55,77,84,85]. In support of this, several studies including our own, have shown that membrane SFAs, fasting glucose, C-reactive protein, and adipokines including adiponectin and resistin are increased but leptin is decreased in patients with recent onset PDs[28,39,57,86-89]. Evidence suggests that while all fatty acids can inhibit adipokine/leptin production, effect of SAFs could be detrimental[12,57,89,90]. In addition, elevated SAFs in adipocytes and intercalated macrophages can stimulate *de novo* biosynthesis of ceramides, which can further potentiate inflammatory effect of SFAs in adipose tissue by disrupting adipokine secretion and signaling in patients with PDs[21,86,91,92]. Moreover, adipose tissue abnormalities are directly associated with cardio-vascular dysfunctions in obese individuals; therefore, cardio-vascular dysfunction in patients with PDs could be influenced by both impaired membrane fluidity of vascular endothelial cells as well as adipose tissue abnormalities most likely induced by elevated SFAs synthesized *via* DNL[53,55,93].

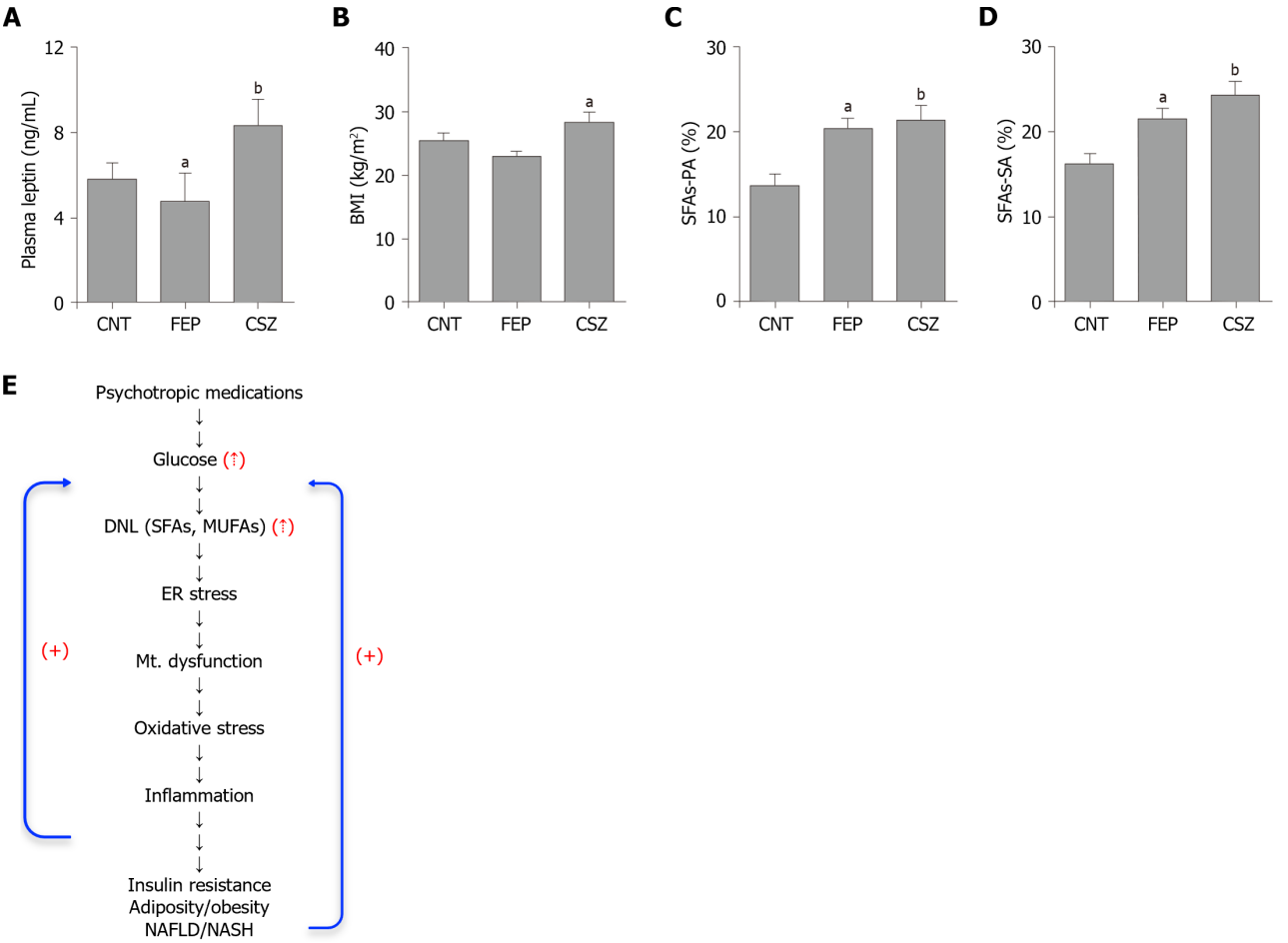

Figure 1 Influence of antipsychotic drugs on metabolic parameters. A: Plasma leptin in control subjects, drug-naïve first-episode and antipsychotic-treated chronic schizophrenia patients; B: Body mass index; C: Saturated fatty acids (SAFs)-palmitic acid; D: SFAs-stearic acid in the same groups; E: Psychotropic medications increase stimulate SAFs and monounsaturated fatty acids levels by increasing *de novo* lipogenesis. SFAs can induce endoplasmic reticulum stress, mitochondrial dysfunction and development of various metabolic abnormalities including insulin resistance, adiposity/obesity, and non-alcoholic fatty liver disease/steatohepatitis. Red arrows indicate increase, and blue arrows indicate stimulatory (+) effect of oxidative stress and inflammation on *de novo* lipogenesis and various metabolic abnormalities. CNT: Control; FEP: First-episode; CSZ: Chronic schizophrenia; BMI: Body mass index; SFAs-PA: Saturated fatty acids-palmitic acid; SFAs-SA: Saturated fatty acids-stearic acid; SFAs: Saturated fatty acids; MUFAs: Monounsaturated fatty acids; ER: Endoplasmic reticulum; DNL: *De novo* lipogenesis; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; Mt: Mitochondrial. Citation for Figure A-D: Khan MM. Disrupted leptin-fatty acid biosynthesis is an early manifestation of metabolic abnormalities in schizophrenia. *World J Psychiatry* 2022; 12: 827-842.

PSYCHOTROPIC MEDICATIONS TRIGGER THE DEVELOPMENT OF NAFLD

Over the years several authors have investigated the prevalence of liver disease before and after treatment with psychotropic medications in patients with PDs. The available data suggests that a great majority of patients with PDs possess pre-existing risk of developing NAFLD/non-alcoholic steatohepatitis (NASH) within 1-3 years following treatment with psychotropic medications[7,94-96]. Epidemiological studies have shown that extent of NAFLD/NASH prevalence may vary from 27% in United States to as high as 50% in China in patients with PDs compared to the general population. And evidence suggest that the onset of NAFLD/NASH could be positively associated with circulating triglycerides, body mass index, combination and dosage of psychotropic medications, and clinical symptoms in PDs[94-97].

Liver inflammation/NAFLD, irrespective of the cause, is triggered by the dysregulation of DNL leading to lipid/fatty acid accumulation within the hepatocytes[45]. In PDs, whether increased prevalence of NAFLD/NASH is associated with enhanced DNL remains to be validated. However, recent studies have shown that increased plasma and liver free fatty acids and TGs in normal population with NAFLD/NASH are primarily a result of enhanced DNL in liver. Since treatment with both APs and ADs increases plasma free fatty acid, TGs, and the risk of NAFLD/NASH; therefore, enhanced DNL could be a major risk factor associated with the development of NAFLD/NASH in patients with PDs[7,45,95,96,98,99].

As discussed before, several lines of evidence suggest that insulin resistance could be a potential risk factor for developing PDs[66]. Insulin resistance also strongly stimulates hepatic DNL leading to lipid/fatty acid accumulation and development of NAFLD/NASH[37,68,100]. Since, insulin resistance may develop from the early childhood age in patients with PDs, as a consequence, DNL could also be enhanced coinciding with the development of insulin resistance [66]. Although increased SFAs, synthesized *via* DNL, can activate several pro-inflammatory pathways associated with

insulin resistance, they can also be incorporated into membrane phospholipids resulting into reduced membrane fluidity, which can further potentiate inflammatory response and hepatic insulin resistance and progression to NAFLD/NASH, and this could be a likely scenario after treatment with psychotropic medications in patients with PDs. Further, evidence suggest that excess SFAs and TGs produced by liver DNL could be released in circulation, and can activate adipocytes and blood immune cells, specially, monocytes leading to further potentiation of pro-inflammatory cues in patients with PDs[45,98,100,101].

MECHANISM(S) OF PSYCHOTROPIC MEDICATION-INDUCED ADIPOSITY/OBESITY AND NAFLD

Regarding the mechanism(s) associated with the development of various metabolic abnormalities by psychotropic medications, elevated fatty acids/lipids (SFAs, MUFAs, TG) and leptin together can activated/alter multiple signaling pathways involved in oxidative stress, inflammation and development of various metabolic abnormalities in PDs[12,18,19,59]. Although it is not clear how psychotropic medications increase fatty acid/lipid and leptin synthesis, disruption of calcium homeostasis/signaling could be the major causative factors because; both APs and ADs have been shown to block/inhibit various voltage-gated and non-voltage gated calcium channels, and calcium supplementation has been shown to significantly reverse the early weaning-induced metabolic abnormalities including hyperleptinemia in adult animals[102-106]. Also, several studies have shown that calcium supplementation reduces plasma leptin production (increased leptin production beyond physiological limit is positively associated with obesity), and development of obesity and NAFLD in obese individuals and laboratory animals[106-109]. Thus, while the above findings suggest that psychotropic medications may increase leptin synthesis, body weight and the extent of NAFLD in patients with PDs, it could be a result of perturbed calcium signaling/availability.

An overwhelming body of evidence suggests that elevated SFAs can disrupt insulin signaling and energy homeostasis by altering ER and mitochondrial function (Figure 1). Cell culture studies have shown that treatment with SFAs causes abrupt release of Ca^{2+} from ER thereby depleting ER Ca^{2+} store. This leads to a sharp increase in cytosolic and mitochondrial Ca^{2+} concentration mediated by store-operated Ca^{2+} channels[19]. This process has been shown to increase reactive oxygen species formation as a consequence of ER stress and mitochondrial dysfunction (Figure 1). Further, several studies have shown that SFAs, particularly, palmitic acid can induce ER stress in a variety of distantly related cells and tissues including pancreas, adipose tissue, and brain by altering Ca^{2+} homeostasis[19].

It has been shown that SFAs-induced activated adipocytes as well as macrophages, mainly, inflammatory type (M1 type) play a major role in inflammation by producing several pro-inflammatory cytokines including interleukin (IL)-1b, IL-6, IL-8, and TNF-α[19]. Since SAFs have been shown to increase these pro-inflammatory markers, and SFAs are further increased after treatment with psychotropic medications, which therefore could be a major contributing factor in the development of pro-inflammatory response and metabolic abnormalities during long-term treatment with psychotropic medication in patients with PDs[36,58-61].

Several lines of evidence suggest that elevated leptin can induce adiposity/fat mass accumulation. It has been shown to potentiate inflammatory, lipogenic, and adipogenic response in cellular and animal models[110-112]. Leptin treatment of adipocytes has been shown to increase the synthesis of various inflammatory cytokines including TNF-α, IL-10, and IL-6 [110]. Evidence suggest that together with TNF-α, leptin can activate macrophages leading to increased secretion of inflammatory cytokines, which may further amplify inflammatory response[113-115]. Also, leptin either alone or in association with TNF-α can induce inflammation of the pancreas disrupting β-cell function and insulin secretion[110,116,117], a scenario typically seen in patients with PDs after long-term treatment with psychotropic medications.

Adipogenic effect of leptin could be enhanced further by increased DNL and adiposity/obesity[110]. It has been shown that leptin can increase the production of PLIN1, CAV-1, PPARγ, SREBP1C, and/or adiponectin[110]. These proteins together increase transcription of various genes involved in adipocyte differentiation. Regarding the signaling pathways involved in lipogenic effect, evidence suggest that leptin can increase lipid accumulation in adipocytes *via* mechanistic target of rapamycin-dependent pathway[110], which may occur even without insulin action that is crucial for pre-adipocyte differentiation. These findings suggest that leptin may stimulate adipocyte differentiation and DNL even in the absence of insulin signaling. In support of this, it has been shown recently that removing circulating plasma leptin can reduce body weight and hyperglycemia in obese rats[112]. This is an interesting outcome, which may lead to designing leptin-based treatment for reducing obesity and diabetes develop during long-term treatment with psychotropic medications.

Regarding the role of leptin in the development of NAFLD, elevated leptin has been associated with the increased risk of NAFLD. In one study, analysis of 4571 patients with NAFLD, leptin level progressively increased with the increase in the severity of NAFLD[118]. Although, some report suggests that higher leptin level may be protective against NAFLD, result of recent meta-analyses suggest that elevated leptin could be a potential risk factor for developing NAFLD[119,120]. Moreover, since leptin elevation is strongly associated with obesity, and obesity is positive associated with NAFLD; therefore, it can be hypothesized that hyperleptinemia in obese individuals may accelerate the development of NAFLD, a scenario that most likely develops during long-term treatment with psychotropic medication in patients with PDs.

CLINICAL IMPACT AND THERAPEUTIC CONSIDERATIONS

Although psychotropic medications are the first line of treatment for PDs, as discussed above that their long-term use can induce or exacerbate various metabolic abnormalities including insulin resistance/diabetes, obesity, and NAFLD[7,8,72-

Table 3 Effect of selective adjunctive/anti-inflammatory drugs on symptoms of psychosis, depression, insulin resistance and non-alcoholic fatty liver disease

Agents/drugs	Psychosis[1]	Depression[2]	Insulin resistance[3]	NAFLD[4]
Aspirin	Reduced[136,137]	Reduced[142]	Reduced[151]	Reduced[160]
N-acetylcysteine	Reduced[136,137]	Reduced[143]	Reduced[152]	Reduced[161]
Minocycline	Reduced[136,137]	No change[144]	Reduced[153]	Increased[162]
Pregnenolone	Reduced[137]	Reduced[145]	?	Reduced[163]
Estrogens	Reduced[136,137]	Reduced[146]	Reduced[154]	Reduced[164]
Raloxifene	Reduced[137]	?	May reduce[155]	Reduced[165]
Curcumin	Reduced[138]	Reduced[147]	Reduced[156]	Reduced[166]
Pioglitazone	Reduced[139]	Reduced[148]	Reduced[157]	Reduced[167]
Celecoxib	Reduced[140]	Reduced[149]	Reduced[158]	Reduced[168]
w3-PUFAs	Reduced[141]	Reduced[150]	Reduced[159]	Reduced[169]

[1]Measure of positive and negative syndrome scale score.
[2]Measure of Hamilton depression rating scale total scores.
[3]Measure of insulin resistance and hyperglycemia.
[4]Non-alcoholic fatty liver disease is positively associated with *de novo* lipogenesis; thus, reduced non-alcoholic fatty liver disease indicates a decrease in *de novo* lipogenesis.
NAFLD: Non-alcoholic fatty liver diseases; w3-PUFAs: w-3 polyunsaturated fatty acids.

75,95,96,121-123]. Even early intervention with psychotropic medications has been shown to trigger the development of various metabolic abnormalities in children and adolescents with PDs[124,125]. The mechanism(s) underlying these metabolic abnormalities remains to be documented; however, as discussed before that DNL dysregulation leading to fatty acid accumulation could be the likely mechanisms involved[7,12,57]. In support of this, several studies have shown that the levels of RBC's SFAs and MUFAs are increased in patients with PDs after treatment with psychotropic medications compared to the untreated patients or control subjects[36,39,58,61]. Since RBC's fatty acid (SAFs and MUFAs) composition can be used to assess the extent of DNL in health and diseases, increased RBC's SAF and MUFA levels by treatment with psychotropic medications suggest that DNL could be enhanced[12,46,51,57]. In support of this, several intermediary metabolites used in DNL including lactate, pyruvate, glutamate and glutamine among others are increased after treatment with psychotropic medications[126-135] (Table 2). Thus, while these evidences suggest that targeting DNL could be an effective strategy for minimizing the risk of developing/exacerbating various metabolic abnormalities following long-term treatment with psychotropic medications, data from preliminary clinical trial studies conducted with various adjunctive drugs that reduce NAFLD/NASH strongly support this notion (Table 3).

In the last two decades, several combination therapy trials have been conducted with adjunctive drugs including anti-inflammatory agents and anti-oxidants in PDs[136-139]. Addition of these adjunctive drugs to the clinically approved doses of APs or ADs have been shown to reduce symptoms of psychosis and depression (Table 3). While these agents also reduce insulin resistance, evidence suggests that this effect could be a result of reduced DNL as evident by decrease in NAFLD/NAD (Table 3). Among these agents, aspirin, minocycline, N-acetylcysteine, pregnanolone, estrogen, raloxifene (estrogen receptor modulators), and curcumin have been found to reduce NAFLD/DNL in various experimental studies (Table 3). Development of NAFLD can affect multiple systems and is associated with various metabolic abnormalities including dyslipidemia, insulin resistance, obesity, and cardiovascular diseases and is triggered primarily by dysregulated DNL[50,170,171].

As shown in Table 3, that most of the adjunctive drugs, mentioned above, have been shown to reduce NAFLD in various experimental studies. These findings, together with the favorable effects of these drugs on symptoms of depression and psychosis suggest that enhanced DNL could be an intrinsic risk factor associated with the etiopathology of PDs. Therefore, large randomized clinical trials with therapeutic agents that inhibit/regulate DNL are warranted. In this context, excellent recent reviews by Batchuluun *et al*[34], and Jeon *et al*[35] which have presented a detailed account of functional and clinical significance of various DNL inhibitors, can be considered.

Since the evidence discussed earlier suggests that enhanced DNL could be the primary mediator of insulin resistance, which may develop from the early childhood age in patients with PDs; therefore, early intervention with appropriate therapeutic agents that regulate/inhibit DNL may reverse/normalize cellular signaling(s) that leads to the development of brain and peripheral tissue inflammation, and various metabolic abnormalities in patients with PDs. For early intervention, some adjunctive drugs, namely, N-acetylcysteine, pioglitazone or curcumin can be given preference over others[12]. N-acetylcysteine has been shown to reduce most of the psychotic symptoms, inflammation, insulin resistance and NAFLD, while having positive effect on cognition and neurogenesis (Table 3). Although, estrogen has been found effective in reducing psychosis, possible induction of feminization effect limits its extensive use in men. One the other hand, raloxifene, a synthetic selective estrogen receptor modulator that does not carry the risk of feminization, and

therefore, could be effective both in young men and women with schizophrenia. However, its effectiveness in patients with depression remains to be documented (Table 3). In addition to these agents, curcumin has been shown to reduce inflammation, insulin resistance, and NAFLD while significantly reducing symptoms of depression and psychosis in patients with PDs[138,147,156,166]. These findings together with profound influence of curcumin on neurogenesis and cognition in young and aged rats suggest that it could be worthy of further large-scale clinical trials in patients with PDs [172,173].

CONCLUSION

The evidence discussed above suggests that insulin resistance may develop from the early childhood age in patients with PDs. Since insulin resistance is positively associated with DNL; therefore, DNL could also be enhanced from the early childhood age in patients with PDs. Although elevated intracellular fatty acids (SAFs and MUFAs) synthesized *via* DNL could be the primary mediators of insulin resistance, both insulin resistance and DNL are further deteriorated after treatment with psychotropic medication leading to the development of obesity and NAFLD. This suggests that DNL could be a potential pathological factor associated with various metabolic abnormalities and, targeting DNL could be an effective strategy for reducing the deterioration or development of these metabolic abnormalities and improving global outcome in patients with PDs after treatment with psychotropic medications.

While clinical trial(s) with specific DNL inhibitor(s) have not been performed, various adjunctive drugs used in combination with psychotropic medications in treating patients with PDs have been shown to reduce the development of insulin resistance and NAFLD in laboratory animals (Table 3). Some of these adjunctive drugs, namely, N-acetylcysteine, pioglitazone and curcumin have satisfactory safety profiles and are therefore worthy of early intervention and long-term use in PDs. Regarding the early intervention, since insulin resistance is potential a risk factor for developing PDs and could be diagnosed during childhood stage or before the onset of classical symptoms in patients with PDs; therefore, early intervention with an appropriate adjunctive drugs or other therapeutic agents that reduced/regulate DNL and insulin resistance may normalize cellular signaling/mechanism, which leads to the development of various metabolic abnormalities in patients with PDs.

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FOOTNOTES

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Country of origin: India

ORCID number: Mohammad M Khan 0000-0001-5973-447X.

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