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Commentary

COMMENTARY

Current and Novel Approaches to Mitigate Cardiometabolic Adverse Effects of Second-Generation Antipsychotics

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Abstract

Second-generation antipsychotic–related weight gain and metabolic disturbances are a major public health issue given the widespread prescribing of these medications. The lack of clearly known mechanisms of cardiometabolic adverse effects and the relevance of cardiometabolic health for survival make this an important area for research. While nonpharmacologic and some pharmacologic treatments have shown benefits vs control conditions or placebo, the effects are modest and long-term benefits are less clear. Therefore, new approaches to mitigate second-generation antipsychotic–associated cardiometabolic burden are sorely needed.

Key Words: Tat-3L4F, second-generation antipsychotics, cardiometabolic risk, gut microbiota

Antipsychotic Treatment and Cardiometabolic Risk

The use of the second-generation antipsychotics (SGAs) carries significant risk of cardiovascular disease (CVD) not only by association but also causation (García-Tornadú et al., 2010; Scigliano and Ronchetti, 2013). SGA use has been associated with weight gain, dyslipidemia, and type 2 diabetes (Maayan and Correll, 2011; De Hert et al., 2012). Their negative cardiometabolic impact is of major concern in light of increased worldwide off-label use in the last decades (Correll et al., 2011; Hirsch and Pringsheim, 2016). CVD significantly affects severe mentally ill (SMI) (De Hert et al., 2018; Taipale et al., 2018) and thus their overall quality of life (Reininghaus et al., 2015; Hayes et al., 2017).

The mechanism via which SGAs induce adverse effects is complex and poorly understood, however intensively studied (De Hert et al., 2012). Glucometabolic side effects may directly induce insulin resistance acting on insulin-dependent organs and hypothalamic-liver circuit and dysregulate hypothalamic food intake centers, resulting in increased energy intake and adiposity (Ballon et al., 2014). SGA-induced obesity

elevates the concentration of free fatty acids and inflammatory markers, both diminishing the insulin sensitivity (Chen et al., 2017). Moreover, SGAs may negatively disrupt gut microbiota (Skonieczna-Żydecka et al., 2019), conferring disadvantages to the host metabolism (Heiss and Olofsson, 2018).

Main Strategies to Diminish SGA Side Effects Include Both Pharmacological and Lifestyle Interventions

Every patient (and her or his family physician), shortly after SGA initiation, should be informed about the risk of cardiovascular adverse effects but also receive means for intervention to counteract potential side effects, even in case of unclear efficacy (Figure 1; Stroup and Gray, 2018). The SMI population requiring SGAs should be regularly assessed for diabetes, body mass index (BMI), waist circumference, fasting glucose (or hemoglobin A1C) and lipid levels, and blood pressure. However, monitoring rates in clinical practices have been suboptimal but stable over time (Mitchell et al., 2012).

Lifestyle Interventions

Lifestyle interventions should be initiated before pharmacological treatments and, if insufficient alone, be continued together (Cooper et al., 2016). As meta-analyzed by Speyer et al. (Speyer et al., 2019), a group of 4267 psychotic patients benefited statistically from physical activity and dietary approaches supported by behavioral counselling. The overall effect size on BMI was –0.63 (95% confidence interval [CI] = –1.02,–0.23; $P = .002$) with identical but nonsignificant effect size of –0.63 at follow up. The chance to decrease weight by at least 5% of initial body weight increased by one-half (relative risk [RR] = 1.51, 95% CI = 1.07, 2.13; $P = .02$). However, given the high degree of obesity in the SMI, the overall effects were interpreted as clinically insufficient (Speyer et al., 2019). The Mediterranean diet is recommended in lipid disorders (Bagetta et al., 2020). It includes fiber source and the reduction in the intake of proinflammatory nutrients, such as trans and saturated fatty acids (Ruiz-Núñez et al., 2016) or simple sugars, especially fructose, which enhances intrahepatic fat synthesis and insulin resistance (Rippe and Angelopoulos, 2016). The desired goal is to lose about 5% to 10% of the initial body weight over a 6-month period, which can increase insulin sensitivity by 30% to 60% (Hoyas and Leon-Sanz, 2019). The Mediterranean diet lifestyle includes moderate physical activity (Alvarez-Alvarez et al., 2018). In a recent study, 4 trainings per week, 45 minutes each, improved the cardiometabolic fitness in schizophrenia patients (Curcic et al., 2017). As recommended by the European Psychiatric Association (Stubbs et al., 2018), both aerobic and anaerobic activities (heart rate ≤85% of maximum) should be advised.

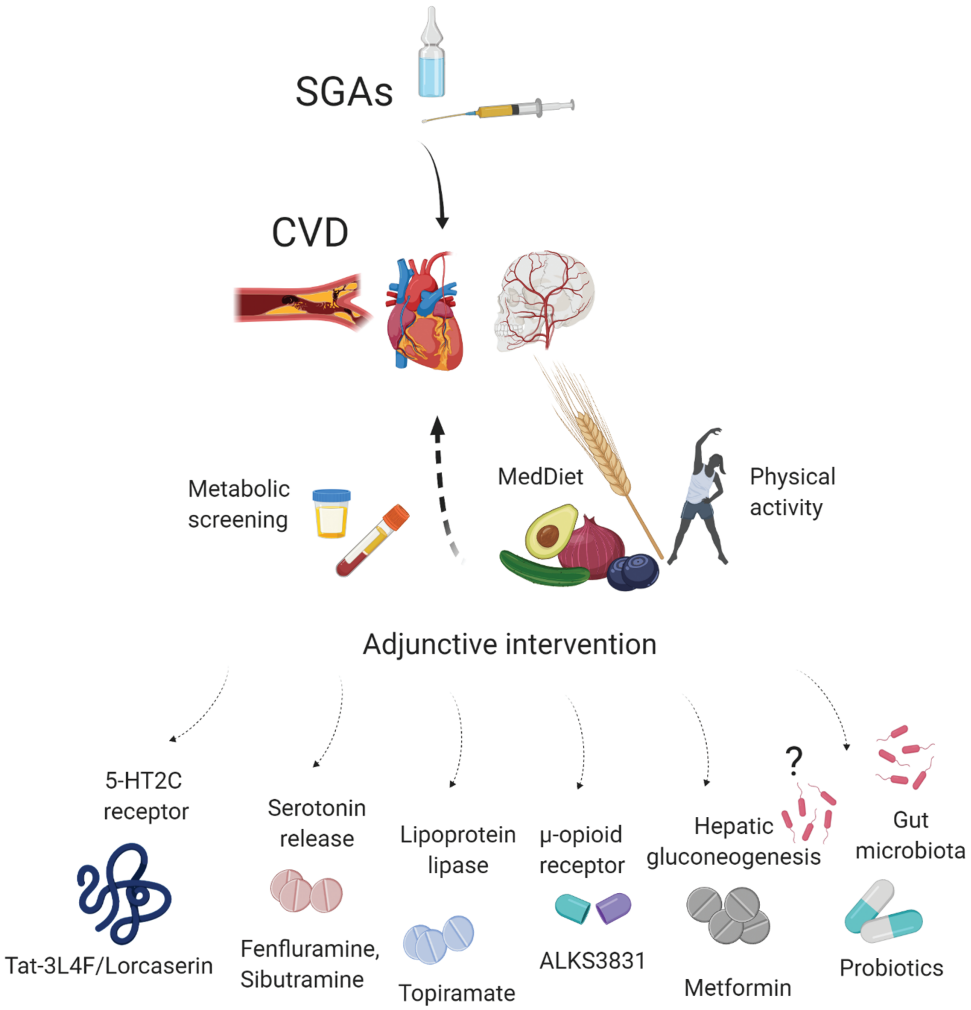

Figure 1. Potential add-on interventions to counteract second-generation antipsychotic (SGA)-induced metabolic dysregulation.

Pharmacological Interventions

To ameliorate SGA-induced cardiometabolic impairments, lowering the dose and switching to a lower risk antipsychotic can be used (Keks et al., 2019). The latter might significantly decrease BMI (z-score change from baseline: –0.11 ± 0.04, $P = .001$) compared with controls continuing a baseline SGA regimen (Correll et al., 2020). Furthermore, implementing adjunctive pharmacologic agents is frequently utilized, although, overall, such trials have had modest success (Vancampfort et al., 2019). To counteract SGA-induced weight changes, metformin has been the most extensively studied adjunctive medication inhibiting hepatic gluconeogenesis and thus improving the sensitivity of insulin in skeletal muscles (Zheng et al., 2017). The drug was demonstrated to impact the BMI z-score change equal to –0.09 ± 0.03 ($P = .002$) compared with a control group of patients with no add-on drug (Correll et al., 2020).

Other effective options for weight loss include the choice of fenfluramine, sibutramine, topiramate, and reboxetine (Mizuno et al., 2014; Correll et al., 2016) acting as appetite inhibitors via the enhancement of serotonin release stimulation of lipoprotein lipase and inhibition of norepinephrine reuptake, respectively (Dayabandara et al., 2017). However, these pharmacologic interventions may trigger adverse effects, such as lactic acidosis or gastrointestinal complaints in metformin therapy or cognitive blunting during topiramate use (Maayan and Correll, 2011). Among a dozen new drugs that are currently being studied to treat schizophrenia (Krogmann et al., 2019), ALKS3831, the combination of olanzapine plus samidorphan, a μ-opioid antagonist, has been found to significantly reduce the weight gain associated with olanzapine (Martin et al., 2019), which is one of the most weight gain–producing antipsychotics. ALKS-3831 is currently under review with the Food and Drug Administration.

Tat-3L4F: The New Kid on the Block to Counteract SGA-Associated Risk of CVD

In the present issue of IJNP, Wang et al. (2020) described a new intervention with a molecule, Tat-3L4F, whose mode of action includes the agonism-like (allosteric) effects on the serotonin 5-HT2C receptor, which has previously been linked to alleviation of weight gain and hyperphagia (Lord et al., 2017). Interestingly, the suppression of weight gain and appetite together with marked differences in metabolic profile (e.g., increased bile synthesis) came along with phosphatase tensin homolog (PTEN) downregulation in the hypothalamus, which was shown to counteract increased appetite (Sumita et al., 2014). The use of PTEN resulted in reduced body weight, food intake, and blood glucose and lipids in tested rodents. This study is promising due to the unrestricted dopamine influx, as reduced dopamine tone can contribute to cognitive deficits and negative symptoms in mentally ill patients during antidopaminergic therapy (Sullivan et al., 2015). Nevertheless, more studies should elucidate the mechanism of action, potential adverse effects, and clinical efficacy of PTEN. To date, lorcarserin, another 5-HT2C receptor agonist, has been successfully introduced into clinical care. A meta-analysis (Kuo et al., 2020) including 9452 patients indicated that lorcarserin was superior vs placebo, significantly improving anthropometric (weight, BMI, waist circumference), carbohydrate (fasting glucose, HbA1C), and lipid (low-density lipoprotein cholesterol, triacylglycerols) indices along with blood pressure and heart rate. However, long-term stability of these important outcomes is still to be explored, especially regarding other drugs modulating the serotonergic pathway (Singh and Singh, 2020).

Gut Microbiota–Focused Therapy: New Frontier in the Old Battlefield?

An emerging concept within the interventions aimed at improving cardiometabolic health in the SMI has focused on gut microbiota, stimulated by SGA antimicrobial activity, resembling antibiotics (Kristiansen, 1979; Thorsing et al., 2013). The microbial alterations have been linked to cardiometabolic risk (Heiss and Olofsson, 2018; Omer and Atassi, 2017), and SGA-induced changes within gut microbiota could potentially contribute to metabolic adverse events in psychiatric patients (Kanji et al., 2018). As systematically reviewed by us, SGAs were demonstrated to elevate Firmicutes phylum abundance relative to Bacteroidetes, a pattern that is typical for obesity and metabolic malfunctions (Abenavoli et al., 2019). Olanzapine was found to induce adiposity and had an unfavorable impact on serotonin receptors expression, short chain fatty acid synthesis, and inflammation, while risperidone suppressed resting metabolic rate (Skonieczna-Żydecka et al., 2019). Moreover, a favorable effect of prebiotic and probiotic administration on the risk of metabolic and weight disturbances has been reported (Kao et al., 2018; Szulińska et al., 2018). We suggest considering co-administration of pro-/pre-/synbiotic therapy concomitant to SGAs. Based on the emerging data, adding gut microbiome–stabilizing treatment might positively affect host metabolism modulating of (1) fasting glucose, (2) glycated haemoglobin, (3) dyslipidemia, and (4) hypertension in overweight individuals. Target probiotic strains including *Collinsella aerofaciens* were found to be increased in children treated with risperidone but who did not experience weight gain (Bahr et al., 2015). Potential next-generation probiotics include *Akkermansia*, *Bacteroides* spp., and *Eubacterium halli* as well as bacterial structural elements (cell wall proteins) and metabolites (short chain fatty acids) (Romaní-Pérez et al., 2017). Moreover, adjunctive metformin was found to modulate microbiota, resulting in improved propionate and butyrate production and thus glucose homeostasis (Forslund et al., 2015), and to decrease low-grade inflammation in obese individuals (Zhou et al., 2017). In mice receiving metformin, adipose tissue macrophages were found to be polarized to an antiinflammatory M2 phenotype subsequent to AMPK activation (Jing et al., 2018), supporting the hypothesis that inflammation may be crucial for weight gain secondary to SGAs. Metformin was capable of modulating low-grade inflammation in obese animals (Lee et al., 2018). Furthermore, fecal transplants from metformin-treated mice significantly improved metabolic parameters in treated donors. Other agents (e.g., the GLP-1 agonist-liraglutide) not only decreased fasting blood glucose, waist circumference, and HbA1C in schizophrenia patients (Larsen et al., 2017; Khera et al., 2018; Siskind et al., 2019) but also affected gut *Akkermansia* in schizophrenia patients with elevated body mass due to clozapine and olanzapine therapy (Wang et al., 2017). Moreover, dysbiosis is associated with GLP-1 resistance responsible for glucose intolerance and impairment of the brain-gut axis function (Yamane and Inagaki, 2018). Nevertheless, more research is needed to prove the efficacy of microbiome-based therapies in the clinic.

Summary and Conclusions

As the number of SGA prescriptions increases, the SMI population will experience more cardiometabolic effects. Thus, new approaches to mitigate this burden are sorely needed.

Statement of Interest

Christoph U. Correll received speaker's fees, consultancy honoraria, equity ownership, profit-sharing agreements, royalties,

patents, and research grants from industry for which he received compensation for professional services in any of the previous 3 years or from whom he anticipates receiving such compensation in the near future.

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