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INDEXING/ABSTRACTING
The WJP is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJP as 3.500; IF without journal self cites: 3.313; 5-year IF: 7.380; Journal Citation Indicator: 0.62; Ranking: 89 among 155 journals in psychiatry; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Yu-Xi Chen; Production Department Director: Xu Guo; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi, Ting-Shao Zhu, Panteleimon Giannakopoulos

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
August 19, 2022

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LETTER TO THE EDITOR

Cardiotoxicity of current antipsychotics: Newer antipsychotics or adjunct therapy?

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Specialty type: Psychiatry
Provenance and peer review: Invited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0
P-Reviewer: Kusmic C, Italy; Pavón L, Mexico
Received: February 23, 2022
Peer-review started: February 23, 2022
First decision: April 18, 2022
Revised: April 19, 2022
Accepted: July 6, 2022
Article in press: July 6, 2022
Published online: August 19, 2022

Abstract

Use of newer antipsychotics for substitution of current antipsychotics might be one way awaiting to be clinically verified to address antipsychotic cardiotoxic effects. Alternatively, the combination of existing antipsychotics with cardioprotective agents is also beneficial for patients with mental disorders for avoiding cardiotoxicity to the maximum.

Key Words: Antipsychotics; Cardiotoxicity; Combined medication; Adjunct therapy

Core Tip: The newer antipsychotics have been reported to have fewer side effects and better performance in efficacy in short-term studies. Still, a dilemma lies between the benefit of ameliorating psychotic symptoms and severe side effects especially life-threatening cardiotoxicity in antipsychotic medications in clinical practice. The combination of antipsychotics with other therapeutic agents providing cardioprotection, such as β-blockers, cannabinoid 1 receptor antagonists, cannabinoid 2 receptor agonists, spliceosome inhibitors, angiotensin-converting enzyme inhibitors, and ω-3 polyunsaturated fatty acids, may represent a promising strategy and sweet pledge.

Citation: Liu Z, Zhang ML, Tang XR, Li XQ, Wang J, Li LL. Cardiotoxicity of current antipsychotics: Newer antipsychotics or adjunct therapy? World J Psychiatry 2022; 12(8): 1108-1111
URL: https://www.wjgnet.com/2220-3206/full/v12/i8/1108.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i8.1108
TO THE EDITOR

We read with interest a recent paper entitled “Newer antipsychotics: Brexpiprazole, cariprazine, and lumateperone: A pledge or another unkept promise” by Barman et al.[1] published in this journal[1]. The paper appraised the scientific data on psychopharmacology, safety profile, and efficacy of the newer antipsychotics, namely, brexpiprazole, cariprazine, and lumateperone. The authors compared the characteristics and indications of the three newer antipsychotic agents to indicate their promising future in treating schizophrenia in the short term, particularly due to their properties of less metabolic toxicity and potential control of negative symptoms.

In previous studies, several toxic effects were revealed in the use of first-generation antipsychotics and second-generation antipsychotics (SGAs), especially the life-threatening cardiotoxicity. The manifestations of cardiotoxicity range from heart rate change (e.g., bradycardia or tachycardia) and blood pressure alternation (e.g., hypotension or hypertension) to fatal issues such as QT prolongation and congestive heart failure. The three newer antipsychotics mentioned in the article are typical third-generation antipsychotics (TGAs), which display well-documented lower metabolic liability and better performance in targeting negative symptomatology and improving cognitive domains[2]. In addition, some TGAs such as roliperidone are associated with a lower incidence of cardiovascular side effects in short term. However, long-term clinical studies are limited, leading to a deficiency in clinical evidence of TGA cardiotoxicity. Further clinical trials are needed to determine whether TGAs perform better than their precursors in both safety and efficacy.

Given that the clinical application of TGAs is still under debate, the combination of existing antipsychotics with other therapeutic agents in the treatment of mental disorders, especially the cardioprotective agents, may also represent a promising strategy. Several therapeutic agents which are promising in combined medications are listed in Table 1. β-adrenal receptor blockers, as classical antiarrhythmic agents, have been verified to offer symptomatic relief in patients who suffer from tachycardia[3]. Some researchers have reached a consensus that optimal doses of β-blockers like propranolol can be well tolerated and are effective in alleviating clozapine-induced tachycardia and myocarditis[4]. In our serial works, we elaborated that both cannabinoid 1 receptor (CB1R) and cannabinoid 2 receptor (CB2R) were critically involved in SGAs-induced cardiac side effects and played opposite roles in the process of toxicity[5,6]. Administration of SGAs (clozapine or quetiapine) in 2-3 wk caused a decrease in CB1R but an increase in CB2R expression in a dose- and time-dependent manner. The functional rivalry between CB1R and CB2R suggests that specific antagonists of CB1R or agonists of CB2R could relieve antipsychotic cardiotoxicity, such as inflammation suppression and myocardial fibrosis remission. Of note, the opposite effects of cannabinoid receptors suggest that adjunct therapy should be based on single cannabinoid receptor agonism or antagonism since dual agonism/antagonism would unfortunately yield neutralizing effects[7]. In addition, CB1R antagonists have been marketed for weight loss, and CB2R agonists have also been shown to maintain metabolic process[8]. The use of CB1R antagonists or CB2R agonists in combination with antipsychotics might thus exert dual clinical benefits: One to inhibit drug cardiac toxicity and the other to attenuate antipsychotic-induced glycolipid metabolic disorders. Since cardiovascular and metabolic adverse effects compose the major concerns associated with SGAs use, the potential dual benefits derived from CB1R antagonists or CB2R agonists seem to be particularly important in the clinic[9]. However, since individual antagonists of CB1R like rimonabant may cause additional psychiatric disorders due to brain penetration, development of beneficial CB1R antagonists or CB2R agonists that are peripherally restricted could assuage the clinical concerns.

In addition to those G protein-coupled receptor-based adjunct strategies, our recent animal study also suggested that pharmacological inhibition of intracellular spliceosome signaling at a relatively low concentration might also confer cardioprotection against SGAs cardiotoxicity[10]. Since clozapine cardiotoxicity is mainly manifested as cardiac inflammation (myocarditis), inhibition of oxidative stress and proinflammatory cytokines (e.g., tumor necrosis factor-α) were also shown to be protective against clozapine-induced cardiotoxicity[11-13]. Current studies further showed that omega-3 polyunsaturated fatty acids (ω-3 PUFAs) were beneficial for schizophrenia patients in view of its protections against cardiovascular morbidity and mortality[14]. Of note, the dose-related cardioprotective and antiarrhythmic effects of ω-3 PUFAs have been observed in large clinical trials and consequently, this outcome may have provided strong evidence for ω-3 PUFAs becoming a potential candidate in the combined medication[15].

In summary, we are in agreement with the conclusion in the main body of the paper that all three newer antipsychotic agents are promising in the treatment of psychiatric disorders based on short-term studies. However, long-term studies are still limited to provide further evidence for systematic comparison between newer antipsychotics and their precursors. Thus, we put forward that the combination of existing antipsychotics with other cardioprotective agents, such as β-blockers, CB1R antagonists, CB2R agonists, spliceosome inhibitors, angiotensin-converting enzyme inhibitors, and ω-3 PUFAs, may reach the expectation that the combined medication can avoid the severe adverse effects of antipsychotics to the maximum in the treatment of mental disorders. The peripherally-restricted CB1R antagonists or CB2R agonists might merit further large clinical trials since they might provide beneficial control of SGAs-induced both metabolic and cardiac side effects.
Suppressing inflammation, ameliorating myocardial fibrosis

Oxidative stress and proinflammatory cytokine inhibitors

Table 1 Therapeutic agents for potential adjunct therapy in combination with existing antipsychotics

| Therapeutic agents                  | Beneficial effect                                                                 | Ref.  |
|-------------------------------------|----------------------------------------------------------------------------------|-------|
| β-adrenergic receptor blockers      | Alleviating tachycardia and myocarditis                                         | [14]  |
| CB1R antagonists                    | Suppressing inflammation, ameliorating myocardial fibrosis                      | [56]  |
| CB2R agonists                       | Suppressing inflammation, ameliorating myocardial fibrosis                      | [54]  |
| Spliceosome inhibitors (e.g., pladienolide B) | Inhibition of SGAs-induced alternative splicing events and consequent amelioration of inflammation and myocardial cell death | [10]  |
| ACEIs (e.g., captopril)              | Oxidative stress and proinflammatory cytokine inhibitors                        | [11-13]|
| ω-3 PUFAs                           | Anti-arrhythmia                                                                  | [15]  |

ACEI: Angiotensin-converting enzyme inhibitor; PUFAs: Polyunsaturated fatty acids; SGA: Second-generation antipsychotics; CB1R: Cannabinoid 1 receptor; CB2R: Cannabinoid 2 receptor.

FOOTNOTES

**Author contributions:** Liu Z gathered the literature and drafted the manuscript; Zhang ML, Tang XR, Li XQ, and Wang J designed the table; Li LL conceived the original idea and edited the manuscript; all authors participated sufficiently in the work to take public responsibility for its content and provided final approval of the version that was submitted.

**Supported by** National Natural Science Foundation of China, No. 82070285 and No. 81701861.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

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**S-Editor:** Fan JR  
**L-Editor:** Wang TQ  
**P-Editor:** Fan JR

***REFERENCES***

1. Barman R, Majumder P, Doifode T, Kablinger A. Newer antipsychotics: Brexpiprazole, cariprazine, and lumateperone: A pledge or another unkept promise? *World J Psychiatry* 2021; 11: 1228-1238 [PMID: 35070772 DOI: 10.5498/wjp.v11.i12.1228]  
2. Li XQ, Tang XR, Li LL. Antipsychotics cardiotoxicity: What's known and what's next. *World J Psychiatry* 2021; 11: 736-753 [PMID: 34733639 DOI: 10.5498/wjp.v11.i10.736]  
3. Nilsson BM, Edström O, Lindström L, Wernegren P, Bodén R. Tachycardia in patients treated with clozapine vs antipsychotic long-acting injections. *Int Clin Psychopharmacol* 2017; 32: 219-224 [PMID: 28225439 DOI: 10.1097/YIC.0000000000000169]  
4. Wang JF, Min YJ, Hampton TG, Amendé I, Yan X, Malek S, Abelmann WH, Green AI, Zeind J, Morgan JP. Clozapine-induced myocarditis: role of catecholamines in a murine model. *Eur J Pharmacol* 2008; 592: 123-127 [PMID: 18627770 DOI: 10.1016/j.ejphar.2008.06.088]  
5. Li L, Dong X, Tu C, Li X, Peng Z, Zhou Y, Zhang D, Jiang J, Burke A, Zhao Z, Jin L, Jiang Y. Opposite effects of cannabinoid CB1 and CB2 receptors on antipsychotic clozapine-induced cardiotoxicity. *Br J Pharmacol* 2019; 176: 890-905 [PMID: 30707759 DOI: 10.1111/bph.14591]  
6. Li X, Peng Z, Zhou Y, Wang J, Lin X, Dong X, Liu X, Jiang J, Jiang Y, Li L. Quetiapine induces myocardial necroptotic cell death through bidirectional regulation of cannabinoid receptors. *Toxicol Lett* 2019; 313: 77-90 [PMID: 31220554 DOI: 10.1016/j.toxlet.2019.06.005]  
7. Tang X, Liu Z, Li X, Wang J, Li L. Cannabinoid Receptors in Myocardial Injury: A Brother Born to Rival. *Int J Mol Sci* 2021; 22 [PMID: 34206926 DOI: 10.3390/ijms22136886]  
8. Simon V, Cota D. MECHANISMS IN ENDOCRINOLOGY: Endocannabinoids and metabolism: past, present and future.
Liu Z et al. Newer antipsychotics or adjunct therapy?

Eur J Endocrinol 2017; 176: R309-R324 [PMID: 28246151 DOI: 10.1530/EJE-16-1044]

9 De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol 2011; 8: 114-126 [PMID: 22009159 DOI: 10.1038/nrendo.2011.156]

10 Wang J, Li X, Liu Z, Lin X, Zhong F, Li S, Tang X, Zhang Y, Li L. Second-generation antipsychotics induce cardiotoxicity by disrupting spliceosome signaling: Implications from proteomic and transcriptomic analyses. Pharmacol Res 2021; 170: 105714 [PMID: 34098070 DOI: 10.1016/j.phrs.2021.105714]

11 Abdel-Wahab BA, Metwally ME. Clozapine-Induced Cardiotoxicity: Role of Oxidative Stress, Tumour Necrosis Factor Alpha and NF-κB. Cardiovasc Toxicol 2015; 15: 355-365 [PMID: 25539628 DOI: 10.1007/s12012-014-9304-9]

12 Abdel-Wahab BA, Metwally ME, El-khawanki MM, Hashim AM. Protective effect of captopril against clozapine-induced myocarditis in rats: role of oxidative stress, proinflammatory cytokines and DNA damage. Chem Biol Interact 2014; 216: 43-52 [PMID: 24709159 DOI: 10.1016/j.cbi.2014.03.012]

13 Abdel-Wahab BA, Metwally ME. Clozapine-induced cardiotoxicity in rats: Involvement of tumour necrosis factor alpha, NF-κB and caspase-3. Toxicol Rep 2014; 1: 1213-1223 [PMID: 28962331 DOI: 10.1016/j.toxrep.2014.11.012]

14 Scorza FA, de Almeida AG, Scorza CA, Cysneiros RM, Finsterer J. Sudden death in schizophrenia: pay special attention and develop preventive strategies. Curr Med Res Opin 2021; 37: 1633-1634 [PMID: 34060974 DOI: 10.1080/03007995.2021.1937089]

15 Parish S, Mafham M, Offer A, Barton J, Wallendszus K, Stevens W, Buck G, Haynes R, Collins R, Bowman L, Armitage J; ASCEND Study Collaborative Group. Effects of Omega-3 Fatty Acid Supplements on Arrhythmias. Circulation 2020; 141: 331-333 [PMID: 31986094 DOI: 10.1161/CIRCULATIONAHA.119.044165]
