EDITORIAL

1002  Meeting employees where they are: The rise of workplace mental health services

Noy G, Shah RN

REVIEW

1004  Does COVID-19 related symptomatology indicate a transdiagnostic neuropsychiatric disorder? - Multidisciplinary implications

Goldstein Ferber S, Shoval G, Zalsman G, Weller A

ORIGINAL ARTICLE

Case Control Study

1016  Antidepressants combined with psychodrama improve the coping style and cognitive control network in patients with childhood trauma-associated major depressive disorder


1031  Can the prediction model using regression with optimal scale improve the power to predict the Parkinson’s dementia?

Byeon H

Observational Study


Ilic M, Ilic I

1061  Peripartum depression and its predictors: A longitudinal observational hospital-based study

Hamed SA, Elwasify M, Abdelhafez M, Fawzy M

1076  Cross-sectional survey following a longitudinal study on mental health and insomnia of people with sporadic COVID-19

Li XJ, Guo T, Xie Y, Bao YP, Si JY, Li Z, Xiong YT, Li H, Li SX, Lu L, Wang XQ

1088  Fear of COVID-19 and emotional dysfunction problems: Intrusive, avoidance and hyperarousal stress as key mediators


LETTER TO THE EDITOR

1102  Difference between treatment-resistant schizophrenia and clozapine-resistant schizophrenia

Tseng PT, Chen MH, Liang CS

1105  Genetics of adult attachment and the endogenous opioid system

Troisi A
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1108</td>
<td>Cardiotoxicity of current antipsychotics: Newer antipsychotics or adjunct therapy?</td>
<td>Liu Z, Zhang ML, Tang XR, Li XQ, Wang J, Li LL</td>
</tr>
<tr>
<td>1112</td>
<td>Underlying disease may increase mortality risk in users of atypical antipsychotics</td>
<td>Li ZP, You YS, Wang JD, He LP</td>
</tr>
</tbody>
</table>
World Journal of Psychiatry

Contents

Monthly Volume 12 Number 8 August 19, 2022

ABOUT COVER
Editorial Board Member of World Journal of Psychiatry, Rajiv Gupta, MD, Director, Professor, Department of Psychiatry, Institute of Mental Health, Rohtak 124001, Haryana, India. rajivguptain2003@yahoo.co.in

AIMS AND SCOPE
The primary aim of World Journal of Psychiatry (WJP, World J Psychiatry) is to provide scholars and readers from various fields of psychiatry with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJP mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, etc.

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

COPYRIGHT
© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.ff6publishing.com

© 2022 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com
Cardiotoxicity of current antipsychotics: Newer antipsychotics or adjunct therapy?

Zheng Liu, Mo-Lin Zhang, Xin-Ru Tang, Xiao-Qing Li, Jing Wang, Li-Liang Li

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 rolipram 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-adrenergic receptor blockers, as classical arrhythmic 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 agonists 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 assure 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 anti-arrhythmic 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.
**Table 1 Therapeutic agents for potential adjunct therapy in combination with existing antipsychotics**

<table>
<thead>
<tr>
<th>Therapeutic agents</th>
<th>Beneficial effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-adrenergic receptor blockers</td>
<td>Alleviating tachycardia and myocarditis</td>
<td>[34]</td>
</tr>
<tr>
<td>CB1R antagonists</td>
<td>Suppressing inflammation, ameliorating myocardial fibrosis</td>
<td>[56]</td>
</tr>
<tr>
<td>CB2R antagonists</td>
<td>Suppressing inflammation, ameliorating myocardial fibrosis</td>
<td>[56]</td>
</tr>
<tr>
<td>Spliceosome inhibitors (e.g., pladienolide B)</td>
<td>Inhibition of SGAs-induced alternative splicing events and consequent amelioration of inflammation and myocardial cell death</td>
<td>[10]</td>
</tr>
<tr>
<td>ACEIs (e.g., captopril)</td>
<td>Oxidative stress and proinflammatory cytokine inhibitors</td>
<td>[11-13]</td>
</tr>
<tr>
<td>ω-3 PUFAs</td>
<td>Anti-arrhythmia</td>
<td>[15]</td>
</tr>
</tbody>
</table>

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.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Country/Territory of origin:** China

**ORCID number:** Zheng Liu 0000-0001-9105-2268; Mo-Lin Zhang 0000-0002-3055-5555; Xin-Ru Tang 0000-0001-6426-1363; Xiao-Qing Li 0000-0002-3624-2728; Jing Wang 0000-0002-5479-6441; Li-Liang Li 0000-0002-1933-134X.

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

**REFERENCES**

Liu Z et al. Newer antipsychotics or adjunct therapy?


