

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Vortioxetine Treatment for Generalized Anxiety Disorder: A Meta-Analysis of Anxiety, Quality of Life, and Safety Outcomes
AUTHORS	Bin, Qin; Huang, Guangsu; Yang, Qian; Zhao, Mingjun; Chen, Hong; Gao, Wen; Yang, Mingxiu

VERSION 1 – REVIEW

REVIEWER	shaokuan fang Neurology Department, The first hospital of Jilin University, Changchun, China
REVIEW RETURNED	30-Jul-2019

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.
-------------------------	--

REVIEWER	Roger Ho National University of Singapore Singapore
REVIEW RETURNED	07-Aug-2019

GENERAL COMMENTS	<p>Thank you for inviting me to review the paper on “Vortioxetine Treatment for Generalized Anxiety Disorder: A Meta-Analysis of Anxiety, Quality of Life, and Safety Outcomes”. Vortioxetine is a novel antidepressant working on 5HT₇ receptors and increasing acetylcholine. Much of the evidence focuses on the efficacy of vortioxetine on depressive disorder. This meta-analysis on anxiety disorder is welcome. I have the following of publication.</p> <p>1. Under introduction, the authors should mention the relationship between anxiety and chronic medical illnesses. Please add the following statements in line 8.</p> <p>Line 8, ... a major burden on the individual, their family, and health care services.^{2,4} Anxiety is a common comorbidity of chronic medical diseases including atopic dermatitis (Lim et al 2016), asthma (Lu et al 2012), rheumatoid arthritis, (Ho et al 2011), lupus (Mak et al 2011) and stroke (Loh et al 2017). Anxiety has a negative impact on the quality of life of patients suffer from chronic diseases (Ngo et al 2019, Nguyen et al 2019).</p> <p>References</p> <p>Lim VZ et al Anxiety and Depression in Patients with Atopic Dermatitis in a Southeast Asian Tertiary Dermatological Centre. Ann Acad Med Singapore. 2016 Oct;45(10):451-455. PMID: 27832219</p>
-------------------------	---

Lu Y et al Prevalence of anxiety and depressive symptoms in adolescents with asthma: a meta-analysis and meta-regression. *Pediatr Allergy Immunol.* 2012 Dec;23(8):707-15. PMID: 22957535

Ho RC et al Clinical and psychosocial factors associated with depression and anxiety in Singaporean patients with rheumatoid arthritis. *Int J Rheum Dis.* 2011 Feb;14(1):37-47. doi: 10.1111/j.1756-185X.2010.01591.x. Epub 2011 Jan 24. PMID: 21303480

Mak A et al Damage accrual, cumulative glucocorticoid dose and depression predict anxiety in patients with systemic lupus erythematosus. *Clin Rheumatol.* 2011 Jun;30(6):795-803. doi: 10.1007/s10067-010-1651-8. Epub 2011 Jan 11. PMID:21221690

Loh AZ et al The Global Prevalence of Anxiety and Depressive Symptoms Among Caregivers of Stroke Survivors. *J Am Med Dir Assoc.* 2017 Feb 1;18(2):111-116. doi: 10.1016/j.jamda.2016.08.014. Epub 2016 Oct 11. Review. PMID:27742585

Ngo CQ et al Effects of Different Comorbidities on Health-Related Quality of Life among Respiratory Patients in Vietnam. *J Clin Med.* 2019 Feb 7;8(2). pii: E214. doi: 10.3390/jcm8020214. PMID:30736474

Nguyen SH et al Health-Related Quality of Life Impairment among Patients with Different Skin Diseases in Vietnam: A Cross-Sectional Study. *Int J Environ Res Public Health.* 2019 Jan 23;16(3). pii: E305. doi: 10.3390/ijerph16030305. PMID: 30678097

2. Under Introduction, the authors mentioned that “Vortioxetine’s mechanism of action is related to its multimodal activity, which combines two pharmacological properties: direct modulation of receptor activity and inhibition of the 5-HT transporter.” Vortioxetine has other mechanism of action. Please add the following statement:

Line 12 receptor activity and inhibition of the 5-HT transporter. In addition, vortioxetine cause significant increase in the hippocampal Brain Derived Neurotrophic Factors (BDNF) levels as compared with selective serotonin reuptake inhibitors (Lu et al 2018).

Reference:

Lu Y et al Effects of vortioxetine and fluoxetine on the level of Brain Derived Neurotrophic Factors (BDNF) in the hippocampus of chronic unpredictable mild stress-induced depressive rats. *Brain Res Bull.* 2018 Sep;142:1-7. PMID:29933036

3. Under introduction, the authors should mentioned the findings of scientometric analysis. Please add the following statements:

Line 13... Several meta-analyses have proved the efficacy of vortioxetine for the treatment of MDD. A recent scientometric analysis reported the popularity of vortioxetine is on the rising trend (Tran et al 2019)

	<p>Reference:</p> <p>Tran BX et al Indices of Change, Expectations, and Popularity of Biological Treatments for Major Depressive Disorder between 1988 and 2017: A Scientometric Analysis. <i>Int J Environ Res Public Health</i>. 2019 Jun 26;16(13). pii: E2255. doi: 10.3390/ijerph16132255. PMID:31247926</p> <p>4. Under introduction, line 28, the authors mentioned that “Currently there is growing interest in assessing the QoL and functional status impairment in patients with psychological disorders.” Please add references.</p> <p>Currently there is growing interest in assessing the QoL and functional status impairment in patients with psychological disorders (Lee et al 2018, Choo et al 2019).</p> <p>References</p> <p>Lee Y et al Efficacy of antidepressants on measures of workplace functioning in major depressive disorder: A systematic review. <i>J Affect Disord</i>. 2018 Feb;227:406-415. doi: 10.1016/j.jad.2017.11.003. Epub 2017 Nov 7. Review. PMID:29154157</p> <p>Choo CC et al Quality of Life in Patients With a Major Mental Disorder in Singapore. <i>Front Psychiatry</i>. 2019 Jan 18;9:727. doi: 10.3389/fpsyt.2018.00727. eCollection 2018. PMID:3071350</p> <p>5. Under methods (Pg 6), the authors stated that “Based on heterogeneity, data were pooled to estimate the overall effect of all the interventions by random-effect or fixed-effect modelling”. The authors need to explain what random-effect or fixed-effect modelling means?</p> <p>..... random-effect or fixed-effect modelling. Fixed-effect models assume that the population effect sizes are the same for all studies (Cheung et al 2012). In contrast, random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Ho et al 2010).</p> <p>References:</p> <p>Cheung MW et al. Conducting a meta-analysis: basics and good practices. <i>Int J Rheum Dis</i>. 2012 Apr;15(2):129-35. PMID:22462415</p> <p>Ho RC et al How to critically appraise and apply meta-analyses in clinical practice. <i>Int J Rheum Dis</i>. 2010 Oct;13(4):294-9. doi: 10.1111/j.1756-185X.2010.01560.x. PMID:21199464</p>
--	--

REVIEWER	Domenico De Berardis NHS, Department of Mental Health, ASL Teramo, Italy
REVIEW RETURNED	31-Aug-2019

GENERAL COMMENTS	In the present study, the Authors conducted a SR and a meta-analysis to estimate the efficacy, safety, and improving QoL and
-------------------------	--

	<p>functional status impairment profiles of vortioxetine treatment of GAD.</p> <p>Overall, I found the study timely, very interesting, well conducted and scientifically sound. PRISMA guidelines were correctly followed. I have only some minor concerns on it:</p> <p>1) In the Introduction, I would suggest Authors to add a brief note on mechanisms of action of vortioxetine especially on GAD and anxiety disorders with appropriate references (see Orsolini et al. Expert Rev Neurother 2016 May;16(5):483-95 and De Berardis et al. J Clin Psychopharmacol. 2017 Dec;37(6):732-734).</p> <p>2) In Methods, page 4 line 18, the Authors wrote "...he decision to include a study was then made by two independent reviewers, after full-text review.". Please add initials of such reviewers if they were Authors or mention them in teh Acknowledgment.</p> <p>3) In Methods, page 5 line 12, the Authors wrote "...the Short Form 36 Health Survey (SF-36) scores as the outcome indicator for QoL to preserve sufficient homogeneity for meta-analysis.". I agree with the Authors, but a brief note as a limitation should be added as some studies hadn't used the SF-36.</p> <p>4) As a general consideration, it is unclear the dosage of VOR effectively working on GAD or other anxiety disorders. It has been hypothesized that 20 mg (or even more) would be more beneficial in anxiety disorders, whereas lower dosages may unaffact or even increase anxiety symptoms. As many studies employed a mean dosage of 10 mg, I would ask the Authors to add a brief note on this point.</p> <p>5) I recommend to check the English language for some typos.</p>
--	--

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: shaokuan fang

Institution and Country: Neurology Department, The first hospital of Jilin University, Changchun, China

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

No comments for the authors

Reviewer: 2

Reviewer Name: Roger Ho

Institution and Country: National University of Singapore, Singapore

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

Thank you for inviting me to review the paper on "Vortioxetine Treatment for Generalized Anxiety Disorder: A Meta-Analysis of Anxiety, Quality of Life, and Safety Outcomes". Vortioxetine is a novel antidepressant working on 5HT7 receptors and increasing acetylcholine. Much of the evidence focuses on the efficacy of vortioxetine on depressive disorder. This meta-analysis on anxiety disorder is welcome. I have the following of publication.

1. Under introduction, the authors should mention the relationship between anxiety and chronic medical illnesses. Please add the following statements in line 8.

Response: Thank you for your suggestion. We have added the following statements in the revision (see page 4 line 8-10).

Line 8, ... a major burden on the individual, their family, and health care services.^{2,4} Anxiety is a common comorbidity of chronic medical diseases including atopic dermatitis (Lim et al 2016), asthma (Lu et al 2012), rheumatoid arthritis, (Ho et al 2011), lupus (Mak et al 2011) and stroke (Loh et al 2017). Anxiety has a negative impact on the quality of life of patients suffer from chronic diseases (Ngo et al 2019, Nguyen et al 2019).

References

Lim VZ et al Anxiety and Depression in Patients with Atopic Dermatitis in a Southeast Asian Tertiary Dermatological Centre. *Ann Acad Med Singapore*. 2016 Oct;45(10):451-455. PMID: 27832219

Lu Y et al Prevalence of anxiety and depressive symptoms in adolescents with asthma: a meta-analysis and meta-regression. *Pediatr Allergy Immunol*. 2012 Dec;23(8):707-15. PMID: 22957535

Ho RC et al Clinical and psychosocial factors associated with depression and anxiety in Singaporean patients with rheumatoid arthritis. *Int J Rheum Dis*. 2011 Feb;14(1):37-47. doi: 10.1111/j.1756-185X.2010.01591.x. Epub 2011 Jan 24. PMID: 21303480

Mak A et al Damage accrual, cumulative glucocorticoid dose and depression predict anxiety in patients with systemic lupus erythematosus. *Clin Rheumatol*. 2011 Jun;30(6):795-803. doi: 10.1007/s10067-010-1651-8. Epub 2011 Jan 11. PMID:21221690

Loh AZ et al The Global Prevalence of Anxiety and Depressive Symptoms Among Caregivers of Stroke Survivors. *J Am Med Dir Assoc*. 2017 Feb 1;18(2):111-116. doi: 10.1016/j.jamda.2016.08.014. Epub 2016 Oct 11. Review. PMID:27742585

Ngo CQ et al Effects of Different Comorbidities on Health-Related Quality of Life among Respiratory Patients in Vietnam. *J Clin Med*. 2019 Feb 7;8(2). pii: E214. doi: 10.3390/jcm8020214. PMID:30736474

Nguyen SH et al Health-Related Quality of Life Impairment among Patients with Different Skin Diseases in Vietnam: A Cross-Sectional Study. *Int J Environ Res Public Health*. 2019 Jan 23;16(3). pii: E305. doi: 10.3390/ijerph16030305. PMID: 30678097

2. Under Introduction, the authors mentioned that “Vortioxetine’s mechanism of action is related to its multimodal activity, which combines two pharmacological properties: direct modulation of receptor activity and inhibition of the 5-HT transporter.” Vortioxetine has other mechanism of action. Please add the following statement:

Response: Thank you for your suggestion. We have added the following statements in the revision (see page 4 line 15-17).

Line 12 receptor activity and inhibition of the 5-HT transporter. In addition, vortioxetine cause significant increase in the hippocampal Brain Derived Neurotrophic Factors (BDNF) levels as compared with selective serotonin reuptake inhibitors (Lu et al 2018).

Reference:

Lu Y et al Effects of vortioxetine and fluoxetine on the level of Brain Derived Neurotrophic Factors (BDNF) in the hippocampus of chronic unpredictable mild stress-induced depressive rats. *Brain Res Bull*. 2018 Sep;142:1-7. PMID:29933036

3. Under introduction, the authors should mentioned the findings of scientometric analysis. Please add the following statements:

Response: Thank you for your suggestion. We have added the following statements in the revision (see page 4 line 18-19).

Line 13... Several meta-analyses have proved the efficacy of vortioxetine for the treatment of MDD. A recent scientometric analysis reported the popularity of vortioxetine is on the rising trend (Tran et al 2019)

Reference:

Tran BX et al Indices of Change, Expectations, and Popularity of Biological Treatments for Major Depressive Disorder between 1988 and 2017: A Scientometric Analysis. *Int J Environ Res Public Health*. 2019 Jun 26;16(13). pii: E2255. doi: 10.3390/ijerph16132255. PMID:31247926

4. Under introduction, line 28, the authors mentioned that “Currently there is growing interest in assessing the QoL and functional status impairment in patients with psychological disorders.” Please add references.

Response: Thank you for your suggestion. We have added the references in the revision (see ref. 21 and ref. 22).

Currently there is growing interest in assessing the QoL and functional status impairment in patients with psychological disorders (Lee et al 2018, Choo et al 2019).

References

Lee Y et al Efficacy of antidepressants on measures of workplace functioning in major depressive disorder: A systematic review. *J Affect Disord*. 2018 Feb;227:406-415. doi: 10.1016/j.jad.2017.11.003. Epub 2017 Nov 7. Review. PMID:29154157

Choo CC et al Quality of Life in Patients With a Major Mental Disorder in Singapore. *Front Psychiatry*. 2019 Jan 18;9:727. doi: 10.3389/fpsy.2018.00727. eCollection 2018. PMID:3071350

5. Under methods (Pg 6), the authors stated that “Based on heterogeneity, data were pooled to estimate the overall effect of all the interventions by random-effect or fixed-effect modelling”. The authors need to explain what random-effect or fixed-effect modelling means?

Response: Thank you for your suggestion. We have explained what random-effect or fixed-effect modelling means (see page 7 line 9-12).

..... random-effect or fixed-effect modelling. Fixed-effect models assume that the population effect sizes are the same for all studies (Cheung et al 2012). In contrast, random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Ho et al 2010).

References:

Cheung MW et al. Conducting a meta-analysis: basics and good practices. *Int J Rheum Dis*. 2012 Apr;15(2):129-35. PMID:22462415

Ho RC et al How to critically appraise and apply meta-analyses in clinical practice. *Int J Rheum Dis*. 2010 Oct;13(4):294-9. doi: 10.1111/j.1756-185X.2010.01560.x. PMID:21199464

Reviewer: 3

Reviewer Name: Domenico De Berardis

Institution and Country: NHS, Department of Mental Health, ASL Teramo, Italy

Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below

In the present study, the Authors conducted a SR and a meta-analysis to estimate the efficacy, safety, and improving QoL and functional status impairment profiles of vortioxetine treatment of GAD. Overall, I found the study timely, very interesting, well conducted and scientifically sound. PRISMA guidelines were correctly followed. I have only some minor concerns on it:

1) In the Introduction, I would suggest Authors to add a brief note on mechanisms of action of vortioxetine especially on GAD and anxiety disorders with appropriate references (see Orsolini et al. Expert Rev Neurother 2016 May;16(5):483-95 and De Berardis et al. J Clin Psychopharmacol. 2017 Dec;37(6):732-734).

Response: Thank you for your suggestion. We have added a brief note on mechanisms of action of vortioxetine especially on GAD (see page 4 line 14-15).

2) In Methods, page 4 line 18, the Authors wrote "...the decision to include a study was then made by two independent reviewers, after full-text review.". Please add initials of such reviewers if they were Authors or mention them in the Acknowledgment.

Response: Thank you for your suggestion. We have added initials of the reviewers (see page 5 line 25).

3) In Methods, page 5 line 12, the Authors wrote "...the Short Form 36 Health Survey (SF-36) scores as the outcome indicator for QoL to preserve sufficient homogeneity for meta-analysis.". I agree with the Authors, but a brief note as a limitation should be added as some studies hadn't used the SF-36.

Response:

Thank you for your suggestion. We have added a brief note for the studies hadn't used the SF-36 (see page 6 line 19-20).

4) As a general consideration, it is unclear the dosage of VOR effectively working on GAD or other anxiety disorders. It has been hypothesized that 20 mg (or even more) would be more beneficial in anxiety disorders, whereas lower dosages may unaffected or even increase anxiety symptoms. As many studies employed a mean dosage of 10 mg, I would ask the Authors to add a brief note on this point.

Response: Thank you for your suggestion. We have discussed the question in Discussion (see page 10 line 7-11).

5) I recommend to check the English language for some typos.

Response: Thank you for your suggestion. We have checked the English language carefully.

VERSION 2 – REVIEW

REVIEWER	Roger Ho National University of Singapore Singapore
REVIEW RETURNED	08-Oct-2019
GENERAL COMMENTS	I recommend publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2

Reviewer Name: Roger Ho

Institution and Country: National University of Singapore, Singapore

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

I recommend publication.

Response: Thank you for your positive comments.