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Review

The potential role of atypical antipsychotics for the treatment of posttraumatic stress disorder☆

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ABSTRACT

Despite the fact that the majority of currently available treatment guidelines propose antidepressants as the first-line pharmacological therapy for posttraumatic stress disorder (PTSD), a substantial portion of patients fail to show an adequate response following this type of treatment. In this context, a number of small, open-label studies and randomized controlled clinical trials (RCTs) have found atypical antipsychotics (AAs) to be a beneficial treatment for patients with PTSD. Thus, the present meta-analysis was conducted to enhance the sample size power and further the current understanding of the role of AAs for the treatment of PTSD. An extensive search of several databases identified 12 appropriate RCTs and available data from 9 of these ($n = 497$) were included in the final meta-analysis. AAs may have potential benefits for the treatment of PTSD as indicated by changes from baseline of the total score on the Clinician Administered PTSD Scale (CAPS; standardized mean difference [SMD] = −0.289, 95% confidence intervals [CIs] = −0.471, −0.106), $P = 0.002$). Additionally, AAs were found to be significantly more effective ($P < 0.0001$) than a placebo in terms of change from baseline for the intrusion sub-score on the CAPS (SMD = −0.373, 95% CIs = −0.568, −0.178) but there were no significant reductions for the avoidance and hyperarousal sub-symptoms. The responder rate and rate of improvement of depressive symptoms were also significantly higher in the AA group than the placebo group ($P = 0.004$ and $P < 0.0001$, respectively). However, the present results should be interpreted carefully and be translated into clinical practice only with due consideration of the limited quality and quantity of existing RCTs included in this analysis.

1. Introduction

Posttraumatic stress disorder (PTSD) is a prevalent and chronic mental disorder that has a high rate of comorbid psychiatric and medical symptoms (Amital et al., 2006; Berry et al., 2013; Chibnall and Duckro, 1994; Kessler et al., 2005; O'Toole et al., 1998; Roy-Byrne et al., 2004). In fact, one in four individuals exposed to trauma is likely to develop PTSD, and most of these patients will require long-term treatment for up to 12–24 months (Bandelow et al., 2012). PTSD patients often experience several domains of symptoms including re-experience of the traumatic event (i.e., intrusion, flashbacks, and nightmares), avoidance (i.e., inability to remember important aspects of the trauma and emotional numbness), and hyperarousal (i.e., irritability, outbursts of anger, difficulty sleeping, and hypervigilance). These symptoms substantially impact an individual's personal, social, financial, and occupational capacities and often cause increases in health care utilization, family disconnection, medical expenses, and public health care costs (Bunting et al., 2013; Eisenman et al., 2003; Leserman et al., 2005).

Most pharmacological guidelines suggest that first-line pharmacotherapy should include selective serotonin reuptake inhibitors

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(SSRIs) and, more recently, venlafaxine extended-release, a serotonin norepinephrine reuptake inhibitor (SNRI), has also been identified as a promising agent for the treatment of PTSD (American Psychiatric Association, 2004; Baldwin et al., 2005; Bandelow et al., 2012; Canadian Psychiatric Association, 2006; Schaffer et al., 2012). However, the current pharmacotherapy options for PTSD often do not result in satisfactory clinical outcomes, as evidenced by several controlled or open-label clinical trials and a handful of meta-analyses that used various selection criteria (Ipser and Stein, 2012; Pae et al., 2008a; Watts et al., 2013). Indeed, a remission rate of 30% and a response rate of 60% for SSRI-treated patients with PTSD can be considered inadequate (Bajor et al., 2011; Ipser and Stein, 2012).

The incidences of psychotic symptoms (defined as hallucinations of all modalities, delusional beliefs, and changes in mood and behavior) identified in PTSD patients by epidemiological studies are relatively high, although they range various from 11 to 67% median rate = 39%; (Berry et al., 2013). These psychotic symptoms are associated with more severe symptomatology and decrease the efficacy of conventional treatments (Berry et al., 2013) which indicates that atypical antipsychotics (AAs) may have a role in the treatment of PTSD. In fact, various AAs have shown positive antidepressant and anti-anxiety effects in a number of small-scale open-label studies (OLSs) and randomized controlled clinical trials (RCTs) (Han et al., 2013; Pae et al., 2013; Pae and Patkar, 2013; Pae et al., 2008b); however, the most largest RCT for PTSD (Krystal et al., 2011) has also failed to separate the efficacy of risperidone from placebo. Although small RCTs and OLSs have demonstrated the potential beneficial effects of AAs for the treatment of PTSD, there is a lack of adequately powered RCTs investigating the efficacy of AAs for treatment of PTSD (Bajor et al., 2011; Pae et al., 2008a).

The current meta-analysis cannot replace a well-designed adequately powered RCT but it can complement available knowledge by pooling data from various small RCTs conducted using a priori inclusion criteria. Moreover, a meta-analysis enables critical comparisons between studies and among competitive drugs as well as achievement of greater statistical power relative to individual trials (Huf et al., 2011). Several meta-analyses have reported favorable results in patients with PTSD following the use of AAs (Ahearn et al., 2011; Ipser and Stein, 2012; Pae et al., 2008a; Watts et al., 2013); however, the majority of large RCTs investigating PTSD (Krystal et al., 2011) failed to find an increased efficacy of risperidone compared to placebo. Furthermore, risperidone did not result in significant improvements in depression and anxiety compared to placebo in these studies.

Therefore, the aim of the present study was to conduct a meta-analysis evaluating the effectiveness and tolerability of AAs for the treatment of PTSD and to further clarify the current position of AAs in this manner based on the most recent RCTs.

2. Methods

2.1. Sources of data

A search of past studies was conducted for AAs (clozapine, olanzapine, risperidone, ziprasidone, quetiapine, aripiprazole, blonanserin, amisulpiride, paliperidone, lurasidone, asenapine, and iloperidone) using key terms associated with PTSD ("post-traumatic", "stress", "disorder", and "PTSD") in the following databases: PubMed, Embase/Medline, PsycINFO, and Cochrane Library. Reference lists from identified articles and reviews were also utilized to find additional studies. Abstracts identified by the literature search were independently screened by two authors of this article (S.M.W. and S.J.L.); potentially eligible papers were then re-evaluated by two other authors (C.H. and C.U.P.) to determine whether they clearly met the selection criteria. If a disagreement occurred, the article in question was discussed and a consensus was reached by the second set of review authors.

2.2. Inclusion criteria for meta-analysis

Only RCTs that prospectively compared one of the searched AAs to a placebo in patients with PTSD diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and that were published in English-language, peer-reviewed journals were included in the present meta-analysis. There were no requirements or restrictions regarding the duration (short-term or long-term) of AA treatment (monotherapy or add-on therapy), comorbidity of symptoms, concomitant medications, presence of psychotic symptoms, severity of PTSD, types of experienced trauma, gender, minimum number of subjects, or treatment basis (i.e., inpatient or outpatient).

2.3. Data extraction for meta-analysis

The characteristics of the participants, treatment details, study procedures, and diagnostic information including comorbid conditions, efficacy measures, dropouts, and adverse events (AEs) were evaluated. Data extraction was first handled by C.U.P. and then reassessed independently by C.H. Mean changes in the rating scales were extracted from the cited studies; if mean changes were not available they were computed. Likewise, if a standard deviation (SD) for the mean change was not available then the weighted median SD from studies in which the SD was reported (or calculations with other available statistical values such as mean 95% confidence intervals (CIs), or t-values) was adopted. The precise extraction of SD data is a crucial point when conducting a meta-analysis and, in fact, if SDs are not available from an original study then that study can be excluded. However, this would drastically reduce the significance of the results via a decrease of statistical power and, therefore, it is an acceptable and commonly used method in this field to produce an estimate based on the weighted average of available studies. Additionally, the quality of the RCTs was assessed using the Jadad score (Jadad et al., 1996).

2.3.1. Primary efficacy measure

The primary efficacy measure was the mean change from baseline of total scores on the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995), which was the most frequently used assessment tool in the included RCTs of PTSD (Bartzokis et al., 2005; Carey et al., 2012; Hamner et al., 2003; Krystal et al., 2011; Padala et al., 2006; Reich et al., 2004; Stein et al., 2002). The change from baseline of total scores on the self-reported Davidson Trauma Scale (DTS) (Davidson et al., 1997) was also included as a primary efficacy measure. The DTS has been demonstrated to be similar to the CAPS regarding scoring procedure and apparent treatment effects, and the score on this scale is considered to be equivalent to the CAPS score (Davidson et al., 2002).

2.3.2. Secondary efficacy measures

The principal secondary efficacy measures were the mean changes from baseline of the sub-scores on the CAPS; intrusion, avoidance, and hyperarousal. Furthermore, responder rates were calculated using the Clinical Global Impression-Improvement (CGI-I) score which were assessed as "much or very much improved" or "no or mild symptoms of PTSD" measured by the total score on the CAPS at the end of treatment. Improvements in depression were also assessed using the mean changes from baseline of the total scores on the Montgomery–Åsberg Depression Rating Scale

(MADRS), the Hamilton Depression Rating Scale (HAM-D), and the Center for Epidemiological Studies-Depression Scale (CES-D).

2.3.3. Safety and tolerability measures

The number of dropouts for any reason and the incidence of AEs related to study medication were also included in the analysis.

2.4. Statistical analysis

Fixed- and random-effects models were applied to the primary and secondary efficacy measure analyses where appropriate. The random-effects model grants more balance than the fixed-effects model because it allows for sampling variability with and between studies, and smaller studies are weighted more while larger studies are weighted less. In general, a random-effects model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is assumed to be identical for all subgroups; this value is computed within subgroups and then pooled across subgroups.

2.5. Effect size

The effect sizes for the primary and secondary efficacy measures in each study are presented as the standardized mean difference (SMD) with 95% CIs because this statistical tool enables combination of the scores from different rating scales. Cohen's classification can be used to evaluate the magnitude of the overall effect size, where a SMD of 0.2–0.5 is a small effect size, a SMD of 0.5–0.8 is a medium effect size, and a SMD greater than 0.8 is a large effect size. The SMDs were calculated using the following equation: [(endpoint mean efficacy score) − (baseline efficacy score)/pooled SD of each treatment group]. An odds ratio (OR) was used for the assessment of binary outcomes, including dropout rates.

2.6. Heterogeneity and sensitivity analyses

Heterogeneity between studies was assessed using the I^2 statistic. This measure evaluates how much of the variance between studies can be attributed to the actual differences between the studies rather than to chance. A magnitude of considerable heterogeneity is usually $I^2 = 75–100\%$. Moreover, sensitivity analyses were conducted to test the robustness of the impact of a single study on the overall results. If a statistical heterogeneity was found by the respective meta-analysis, then subgroup and sensitivity analyses were employed to explore the possible reasons for this heterogeneity. These included judgments regarding whether a single study had a significant impact on the overall estimate or whether an underlying influence attributed to the overall estimate.

2.7. Publication bias

The Egger test was used to evaluate publication bias. This method was adopted because the Egger's linear regression method quantifies the bias captured by a funnel plot using the actual values and precision of the effect sizes while the Begg and Mazumdar's test uses ranks.

2.8. Meta-regression

Additionally, a meta-regression was performed to assess the influence of the moderators: the duration of treatment (less than 8 weeks versus more than 8 weeks), type of treatment (monotherapy versus add-on therapy), type of trauma (combat versus non-combat versus mixed), and antipsychotic type were included as independent parameters influencing the mean changes in the primary and secondary efficacy measures.

2.9. Software package for the meta-analysis

All directly extracted or computed data from the original studies that were included in the present meta-analysis were entered into the Comprehensive Meta-Analysis version 2.0 (CMA v2; Englewood, NJ, USA) software for evaluation.

3. Results

Initially, 12 RCTs (Bartzokis et al., 2005; Butterfield et al., 2001; Carey et al., 2012; Hamner et al., 2009, 2003; Kellner et al., 2010; Krystal et al., 2011; Monnelly et al., 2003; Padala et al., 2006; Reich et al., 2004; Rothbaum et al., 2008; Stein et al., 2002) were identified and thoroughly reviewed for the final meta-analysis (Fig. 1). Given that all of the studies included in the present meta-analysis utilized varied efficacy measures and employed various methods of presenting the results, it was not possible to select data from all of the retrieved studies. Therefore, priority for inclusion in the meta-analysis was given to studies that utilized similar efficacy measures. Three RCTs (Hamner et al., 2009; Kellner et al., 2010; Monnelly et al., 2003) were excluded from the efficacy analysis based on the use of different efficacy measures, publication in abstract form, and/or early termination of the study (Table 1). Thus, data from nine RCTs were included in the final primary efficacy analyses of the meta-analysis (Bartzokis et al., 2005; Butterfield et al., 2001; Carey et al., 2012; Hamner et al., 2003; Krystal et al., 2011; Padala et al., 2006; Reich et al., 2004; Rothbaum et al., 2008; Stein et al., 2002), in which a total of 256 and 241 patients received either AAs or placebo, respectively. The characteristics of the currently available 12 individual studies are summarized in Table 1.

3.1. Primary efficacy

3.1.1. Overall

The results of the meta-analysis regarding primary efficacy are presented as forest plots (Fig. 2). Treatment with AAs was significantly superior to placebo in terms of improvement of global PTSD symptoms, as measured by the mean changes from baseline of total

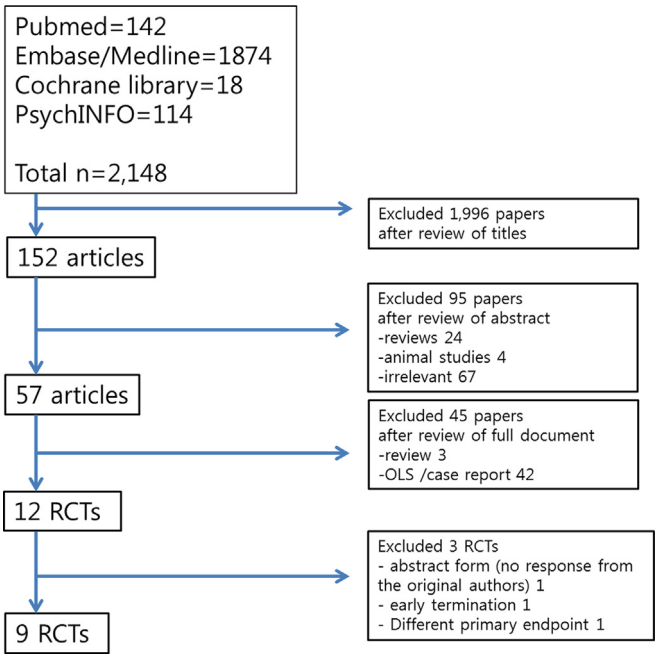

Fig. 1. Flow chart for study selection.

Table 1
Summary of all currently available randomized, double-blind, placebo-controlled clinical trials of atypical antipsychotics (AAs) for the treatment of patients with posttraumatic stress disorder.

Study	JS	Dose (mg/d)	D (weeks)	Sex	Number (AA: PBO)/Age (years)	Major existing medication	Trauma	Psychotic symptoms	Major findings (AA vs. Placebo)	Weight gain	Dropout (AA vs PBO)
Butterfield et al., 2001	3	OZP/14 (mean peak dose)	10	Only 1 M in OZP	10 (44.6): 5 (40.4)	Mono	Mixed	NR	All not significant	11.5 ± 4.43: 0.9 ± 0.06	4 NR for specific group
Stein et al., 2002	3	OZP/15	8	M	10 (55.2): 9 (51.1)	SSRIs	C	NR	CAPS ($p < 0.05$) PSQI ($p = 0.01$) CES-D ($p < 0.03$)	13.2 ± 5.9: −3.0 ± 6.0	3/10: 2/9
Hamner et al., 2003	4	RPR/2.5	5	M	19 (50.8): 18 (53.7)	AD	C	Yes	PANSS ($p < 0.05$) PANSS-GP ($p < 0.05$) CAPS I ($p < 0.05$)	NR	9/19: 6/18
Monnelly et al., 2003[a]	3	RPR/0.6	6	M	8 (48.9): 8 (53.5)	AD	C	NR	OAS-M I ($p = 0.04$) PCL-M ($p = 0.02$) PCL-M I ($p = 0.001$)	NR	1/8: 0/8
Reich et al., 2004	3	RPR/1.4	8	F	12 (30.6): 9 (24.2)	AD	NC	NR	CAPS ($p = 0.015$) CAPS I ($p < 0.001$) CAPS H ($p = 0.006$)	1.1 ± 1.9: 1.4 ± 2.8	3/12: 2/9
Bartzokis et al 2005	3	RPR/3 fixed	16	M	33: 32 (51.6 in both group)	AD	C	NR	CAPS ($p < 0.05$) CAPS H ($p < 0.01$) PANSS-P ($p < 0.01$) HAM-A ($p < 0.001$)	NR	11/22: 6/26
Padala et al., 2006	3	RPR/2.6	10	F	11 (39.2): 9 (43.8)	Mono	NC	NR	TOP-8 ($p = 0.03$) CAPS ($p = 0.04$)	NR	2/11: 3/9
Rothbaum et al., 2008	3	RPR/2.1	8	4 M 16 F	14 11	Sertraline 164 mg/d vs. 177 mg/d	NC	NR	CAPS ($p = 0.8$)	NR	5/90: 0/11
Hamner et al., 2009[a]	ND	QTP/258	12	NR	80	Mono	Mixed	NR	CAPS ($p = 0.0070$) CAPS R ($p = 0.0019$) CAPS H ($p = 0.03$) PANSS ($p = 0.0135$) CGI-s (0.003) CGI-i ($p = 0.03$) HAMD ($p = 0.0093$) HAMA ($p = 0.02$)	Not specified	
Kellner et al., 2010[a]	ND	ZIP/40-160	4	NR	24	Sertraline 25–100 mg/d	NR	No	NR	NR	7/24 in total
Krystal et al., 2011	5	RPR/4.0 fixed	24	258 M and 9 F	133 (54.2) 134 (54.5)	AD	C	No	CAPS ($p = 0.11$) MADRS ($p = 0.11$) HAMA ($p = 0.09$) QoL by SF-36 (all not significant)	2.77: 2.8 (lb)	24/133: 25/134
Carey et al., 2012	4	OZP/5-15	8	11 M 17 F	14 14	Mono	NC	No	CAPS ($p = 0.018$) CAPS R ($p = 0.052$) CAPS A ($p = 0.004$) CAPS H ($p = 0.092$) DTS ($p = 0.006$) CGI-s ($p = 0.027$) SDS ($p = 0.004$)	Not specified	5/14: 5/14

Abbreviation: SSRIs, selective serotonin reuptake inhibitors; NR, not reported; CAPS, Clinician Administered PTSD Scale (I, intrusion subscale; H, hyperarousal subscale); PSQI, Pittsburgh Sleep Quality Index; CES-D, Center for Epidemiologic Studies Depression Scale; CGI-I, Clinical Global Impression-Improvement score; PANSS, Positive and Negative Syndrome Scale (P, positive symptom subscale); HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; SIP, Structured interview for PTSD; SPRINT, Short PTSD Rating Interview; DTS, Davidson Trauma Scale; TOP-8, Treatment Outcome PTSD; SDS, Sheehan Disability Scale; OAS-M total score; OAS-M, Overt Aggression Scale-Modified for Outpatients (I, intrusion subscale); PCL-M, Patient Checklist for PTSD-Military Version; MDD, major depressive disorder; SA, substance abuse; M, male; F, female; PBO, placebo; JD, Jadad score; AD, antidepressant; Mon, monotherapy; C, combat; NC, non-combat; ND, not determined.

[a] Not included in the meta-analysis due to not using CAPS or DTS as a primary endpoint, not a full paper and early terminated study for safety issue, respectively.

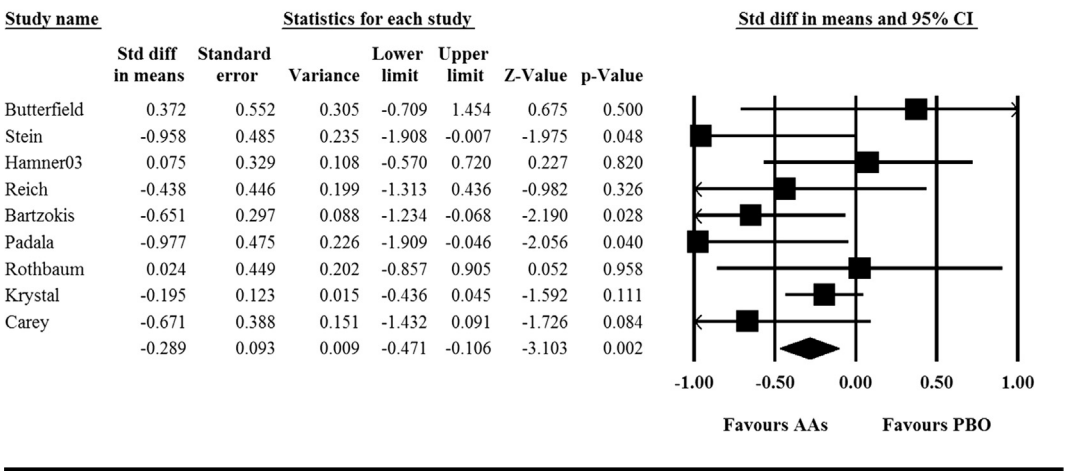

Fig. 2. Meta-analysis of the changes in the CAPS total score from baseline among studies.

scores on the CAPS ($P = 0.002$). The SMD of the mean changes of total scores on the CAPS was also significantly different between the AA and placebo groups, and favored AAs over placebo (SMD = −0.289, 95% CI = −0.471, −0.106). The SMDs from the individual studies ranged from −0.977 to 0.372.

3.1.2. Sensitivity analysis, heterogeneity, and publication bias

The pooled SMDs were repeatedly calculated and analyzed with the omission of one study at a time to perform a sensitivity analysis. The pooled SMDs of the mean change from baseline of total scores on the CAPS ranged from −0.415 to −0.249 when one study at a time was excluded (95% CIs = −0.695, −0.057), which demonstrates that no single study strongly impacted the pooled SMD. The heterogeneity between studies was not significant ($I^2 = 22.2$ %, $P = 0.289$), and the Egger test was not statistically significant ($t = 0.90042$, $P = 0.39781$), suggesting the absence of publication bias.

3.1.3. Meta-regression

There were significant differences among the pooled SMDs regarding the mean change from baseline of total scores on the CAPS according to the moderators, This suggests that the duration of treatment ($Z = 0.25945$, $P = 0.79529$), type of treatment ($Z = 0.96201$, $P = 0.33604$), type of trauma ($Z = -0.96201$, $P = 0.33604$), and antipsychotic type ($Z = 0.90921$, $P = 0.36324$) did not influence the primary treatment outcome.

3.2. Secondary efficacy

3.2.1. Overall

The secondary efficacy outcomes included PTSD cluster symptoms (intrusion, avoidance, and hyperarousal) which were analyzed using six RCTs (Bartzokis et al., 2005; Butterfield et al., 2001; Carey et al., 2012; Hamner et al., 2003; Krystal et al., 2011; Reich et al., 2004), and which are presented as forest plots (Figs. 3–5). Treatment with AAs was significantly superior ($P < 0.0001$) to placebo in terms of changes from baseline of the intrusion sub-score (SMD = −0.373, 95% CI = −0.568, −0.178), but there were no significant reductions of the avoidance (SMD = −0.166, $P = 0.408$) or hyperarousal (SMD = −0.369, $P = 0.088$) sub-scores compared with placebo.

Five RCTs were included in the evaluation of the effects of AAs on depression (Bartzokis et al., 2005; Carey et al., 2012; Krystal et al., 2011; Rothbaum et al., 2008; Stein et al., 2002). A SMD of −0.524 ($P < 0.0001$) indicates a greater improvement in depression, which favored treatment with AAs over placebo. Four RCTs (Butterfield et al., 2001; Carey et al., 2012; Krystal et al., 2011; Stein et al., 2002) were included in the responder analysis. The likelihood of response (OR = 2.432, 95% CI = 1.331, 4.447, $P = 0.004$) in the AA group was significantly greater than in the placebo group.

3.2.2. Sub-score of intrusion

3.2.2.1. Sensitivity analysis, heterogeneity, and publication bias. According to the sensitivity analysis for intrusion, the SMD ranged

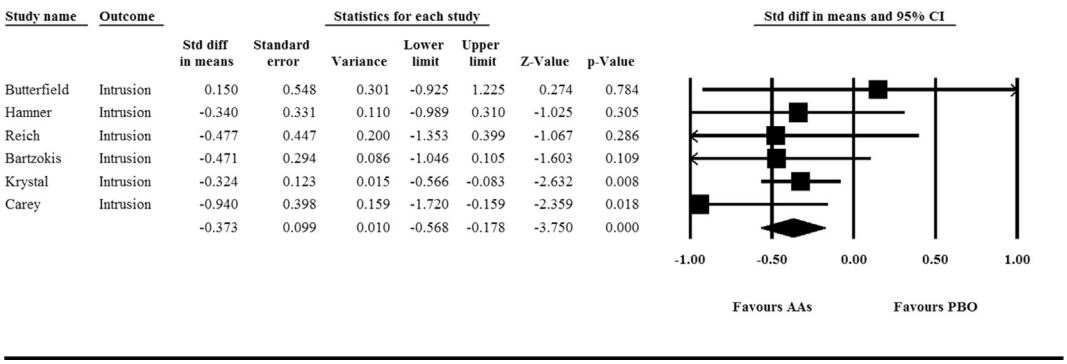

Fig. 3. Meta-analysis of the changes in the CAPS Intrusion sub-scores from baseline among studies.

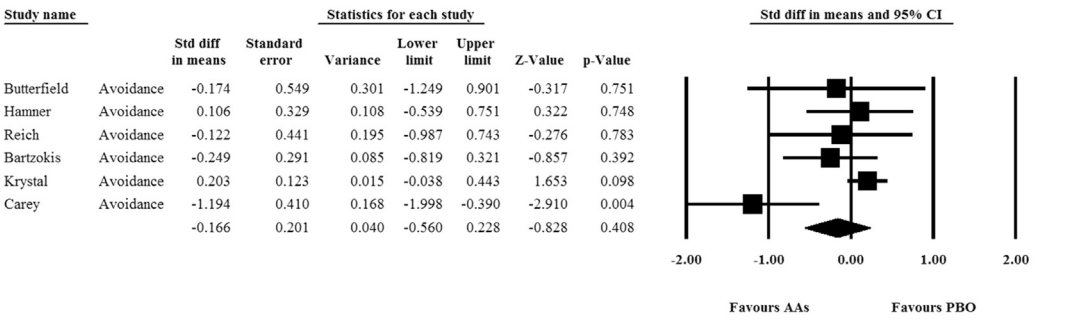

Fig. 4. Meta-analysis of the changes in the CAPS Avoidance sub-scores from baseline among studies.

from −0.463 to −0.335 (95% CIs = −0.793, −0.133) which indicates that no single study strongly impacted the pooled SMD. There was no heterogeneity for intrusion ($I^2 = 0.0\%$, $P = 0.659$) among the studies, and the Egger test was not statistically significant ($t = 0.49005$, $P = 0.64976$), suggesting the absence of publication bias.

3.2.3. Meta-regression

There were no significant differences among the pooled SMDs for intrusion according to the moderators, which suggests that duration of treatment ($Z = 0.93934$, $P = 0.34755$), type of treatment ($Z = 0.62184$, $P = 0.53428$), type of trauma ($Z = -0.13337$, $P = 0.89390$), and antipsychotic type ($Z = 0.62184$, $P = 0.53428$) did not substantially influence the sub-symptom of intrusion.

3.2.4. Sub-score of avoidance

3.2.4.1. Sensitivity analysis, heterogeneity, and publication bias

According to the sensitivity analysis for avoidance, the SMD ranged from −0.309 to 0.107 (95% CIs = −0.742, 0.320), which indicates that no single study strongly impacted the pooled SMD. A significant heterogeneity was seen for avoidance ($I^2 = 58.7\%$, $P = 0.033$) among the studies but the Egger test was not statistically significant ($t = 1.91358$, $P = 0.12822$), suggesting the absence of publication bias.

3.2.4.2. Meta-regression

There were no significant differences in the pooled SMDs for avoidance regarding the duration of treatment ($Z = 1.83014$, $P = 0.06723$); however, the type of treatment ($Z = 2.74379$, $P = 0.00607$), type of trauma ($Z = -2.04464$, $P = 0.04089$), and antipsychotic type ($Z = 2.74379$, $P = 0.00607$) exerted a significant effect. This suggests a differential influence of moderators on the sub-symptom of avoidance.

3.2.5. Sub-score of hyperarousal

3.2.5.1. Sensitivity analysis, heterogeneity, and publication bias

According to the sensitivity analysis for hyperarousal, the exclusion of Butterfield et al. (2001) ($Z = -2.358$, $P = 0.018$) and Hamner et al. (2003) ($Z = -2.652$, $P = 0.008$) changed the results regarding hyperarousal, which suggests that these two studies significantly influenced the pooled SMD of the sub-score for hyperarousal. Likewise, significant heterogeneity was identified for hyperarousal ($I^2 = 63.4\%$, $P = 0.018$) among the studies; however, the Egger test was not statistically significant ($t = 0.40990$, $P = 0.70288$), suggesting the absence of publication bias.

3.2.5.2. Meta-regression

There were no significant differences in the pooled SMDs for hyperarousal according to the moderators, which indicates that duration of treatment ($Z = -0.68673$, $P = 0.49225$), type of treatment ($Z = 0.03040$, $P = 0.97575$), type of trauma ($Z = 0.61067$, $P = 0.54142$), and antipsychotic type ($Z = 0.62184$, $P = 0.53428$) did not substantially influence the hyperarousal sub-symptom.

3.2.6. Depression

3.2.6.1. Sensitivity analysis, heterogeneity, and publication bias

According to the sensitivity analysis for depression, the SMDs ranged from −1.473 to −0.026 (95% CIs = −2.308, 0.852), which

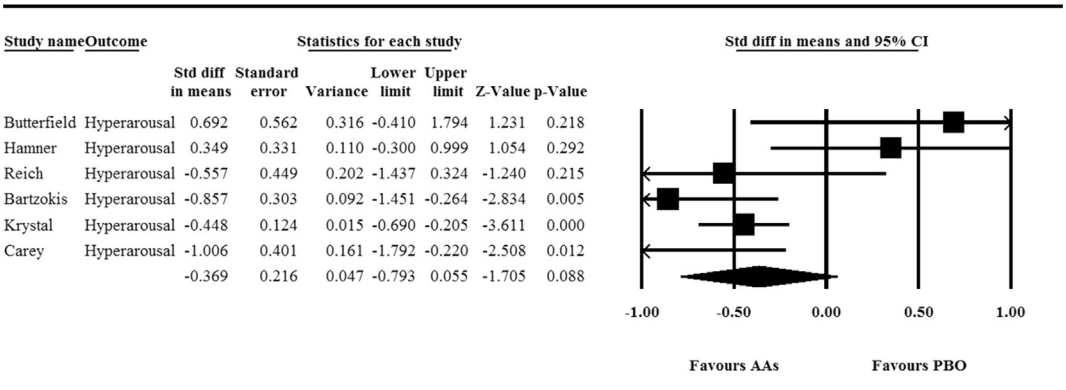

Fig. 5. Meta-analysis of the changes in the CAPS Hyper-arousal sub-scores from baseline among studies.

indicates that no single study strongly impacted the pooled SMD. There was no heterogeneity of the responder rate (I^2 = 54.9%, P = 0.054) among studies, and the Egger test was not statistically significant (t = 0.18698, P = 0.43180), suggesting the absence of publication bias.

3.2.6.2. Meta-regression

There were no significant differences in the pooled SMDs for depression regarding duration of treatment (Z = 0.64409, P = 0.51952), type of trauma (Z = −1.49725, P = 0.13433), or antipsychotic type (Z = 0.98633, P = 0.32397); however, the type of treatment (Z = 2.29762, P = 0.02158) had a significant effect. This suggests a differential influence of moderators on depression.

3.2.7. Responder rates

3.2.7.1. Sensitivity analysis, heterogeneity and publication bias

According to the sensitivity analysis for responder rates, the OR ranged from 2.022 to 3.807 (95% CIs = 1.062, 12.505), which indicates that no single study strongly impacted the pooled OR. There was no heterogeneity of the responder rate (I^2 = 5.3%, P = 0.366) among studies and the Egger test was not statistically significant (t = 0.45722, P = 0.69238), suggesting the absence of publication bias.

3.2.7.2. Meta-regression

There were no significant differences in the pooled OR for the responder rate according to the moderators, which suggests that duration of treatment (Z = −1.53944, P = 0.1237), type of treatment (Z = −0.77400, P = 0.43893), type of trauma (Z = 0.15141, P = 0.87965), and antipsychotic type (Z = −0.85667, P = 0.39162) did not substantially influence the responder rate.

3.3. Safety and tolerability

Safety and tolerability measures were based on dropout rates from the nine RCTs for any reason; dropouts occurred due to AEs in seven RCTs (excluding Carey et al., 2012), and included weight gain in four RCTs (Butterfield et al., 2001; Krystal et al., 2011; Reich et al., 2004; Stein et al., 2002). No significant differences were observed between the AA and placebo groups regarding the likelihood of discontinuation (dropout rates) for any reason (OR = 1.248, 95% CIs = 0.714, 2.183; Fig. 6) or for AEs associated with treatment (OR = 2.493, 95% CIs = 0.867, 7.165; Fig. 7). However, the SMD for weight change was significantly greater in the AA group than in the placebo group (SMD = 1.13, 95% CIs = 0.890, 1.370, P < 0.0001).

4. Discussion

The present meta-analysis demonstrated the potential global efficacy and tolerability of AAs for the treatment of PTSD regardless of the type of administration, duration of treatment, type of trauma, and type of AA. All AAs were found to be significantly superior to a placebo regarding changes from baseline of the intrusion sub-score on the CAPS, but they did not differ in terms of the avoidance or hyperarousal sub-symptoms. Regarding acceptability, the forest plots of dropout rates related to medication compliance demonstrated a favorable trend of treatment with placebo relative to AAs; this trend was not statistically significant. The SMD of the mean change of weight gain revealed a significant and robust difference favoring placebo over AAs. The present findings generally agree with previous research in this respect and support the clinical utility and acceptability of AAs for the treatment of global PTSD symptoms.

However, it is questionable whether the overall SMD of −0.289 (which corresponds to a change of −5.3 points of the total score on the CAPS) between the AA and placebo groups is sufficiently large to be translated into clinical significance. According to a previous study that pooled 13 trials of SSRIs (Ipser and Stein, 2012), a mean difference of −6.6 on the CAPS indicated a modest effect of AAs in PTSD patients. Considering the mean baseline (83.0) and endpoint (60.2) of the total score on the CAPS following treatment with AAs in the present meta-analysis, PTSD patients may suffer at least moderate symptomology. Thus, a 27.5% reduction from baseline of the total score on the CAPS following treatment with AAs indicates that the improvement of PTSD symptoms may be modest, such as from severe to moderate. Furthermore, a trend in the forest plots approached the "line of no effect", which likely represents an additional indicator of "possible borderline efficacy". Among the nine RCTs included in the analysis of the primary efficacy measures,

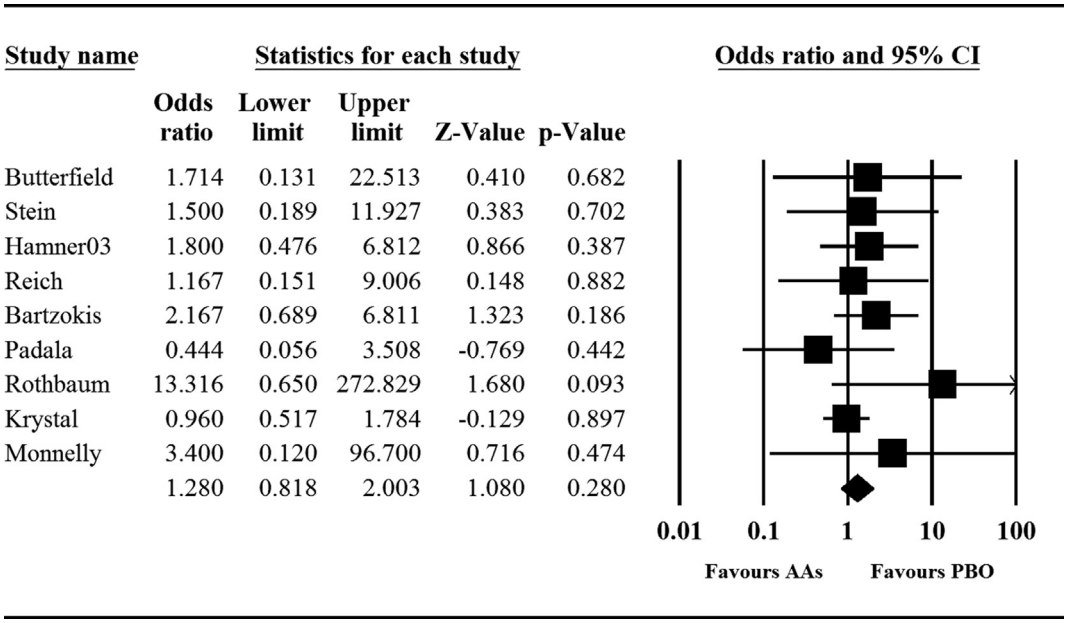

Fig. 6. Meta-analysis of the droup-out rates due to any reason among studies.

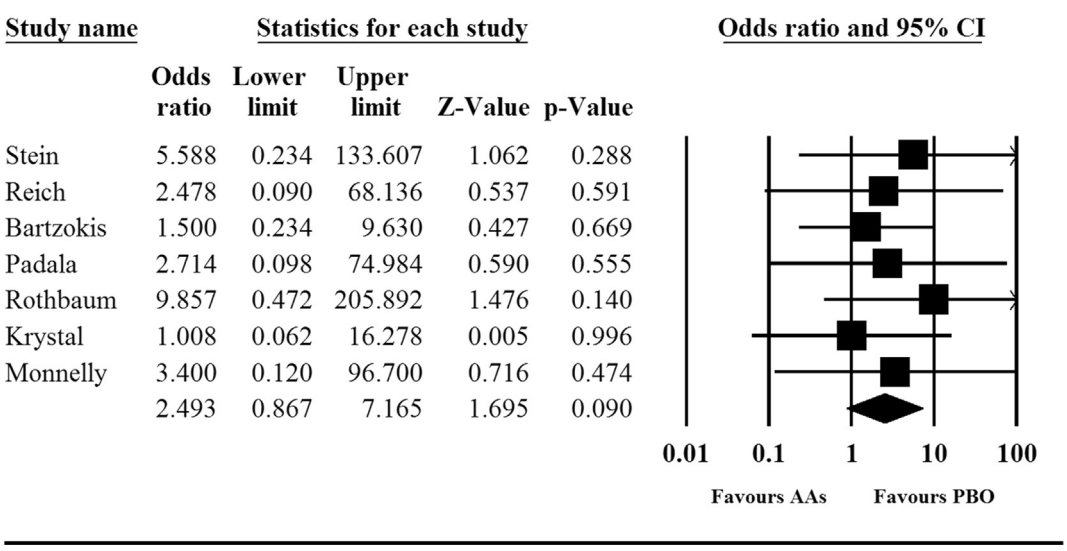

Fig. 7. Meta-analysis of the droup-out rates due to adverse events among studies.

six failed to identify statistically significant differences in the mean change of the total score on the CAPS between the AA and placebo treatments. Moreover, only two RCTs demonstrated a significant difference in the mean change of the total score on the CAPS between the AA and placebo groups, and the benefit of AAs was modest compared to the placebo.

In fact, the most recent and largest RCT, which was conducted by Krystal et al. (2011), failed to identify a robust beneficial effect of 24-week risperidone add-on therapy compared to placebo regarding the reduction of global PTSD symptoms (3.7 point reduction from baseline of the total score on the CAPS favoring risperidone over placebo). Moreover, there were no significant effects concerning depression and quality of life, and AEs were more common following treatment with risperidone than with placebo in terms of weight gain (15.3% versus 2.3%), fatigue (13.7% versus 0.0%), somnolence (9.9% versus 1.5%), and hypersalivation (9.9% versus 0.8%); (Krystal et al., 2011). This study highlights an important clinical issue when using AAs to treat PTSD because PTSD symptoms typically last for an extended period of time and ultimately become chronic and devastating (Kessler et al., 1995). For example, ~40% of PTSD patients exhibit symptoms at 10 years or more after the onset of the disorder. The duration of treatment in that study (Krystal et al., 2011) was clearly long-term compared to previous studies that generally treated patients for 8–12 weeks. Thus, firm conclusions regarding the efficacy of AAs in the short-term versus the long-term cannot be reached because the duration of most successful RCTs was less than 16 weeks; the beneficial effects of AAs may be apparent in the short-term and vanish in the long-term. The establishment of an adequate duration of treatment with AAs should be a future research topic.

An intriguing point introduced by the present meta-analysis is that AAs were effective for the reduction of the intrusion sub-symptom of PTSD but did not significantly influence the avoidance and hyperarousal sub-symptoms. The overall SMD for the three sub-scores of the CAPS was −0.253; however, when the intrusion sub-score was excluded from the analysis this decreased to −0.193, albeit without statistical significance. This suggests that intrusion mainly accounted for the overall effect of AAs on the PTSD sub-symptoms and that AAs may have differential effects on the various symptoms associated with PTSD. Despite the fact that Krystal et al. (2011) failed to identify a significant effect of risperidone compared to placebo regarding the reduction of global PTSD symptoms, risperidone add-on therapy significantly controlled intrusion sub-symptoms. This trend has been consistently reported by a number of previous RCTs in which significant and robust differences in intrusion, but not avoidance and hyperarousal, were identified following treatment with AAs (Bartzokis et al., 2005; Hamner et al., 2003; Krystal et al., 2011; Monnelly et al., 2003; Reich et al., 2004).

Indeed, intrusion has been associated with chronic stressors that may worsen the experience of symptoms and enhance vulnerability to psychosis (Shevlin et al., 2011). It has also been suggested that intrusion has a different neurobiological pathophysiology than avoidance, numbness, and hyperarousal (Blomhoff et al., 1998), and may be more related to psychotic symptoms. This could explain the larger effect of AAs on intrusion symptoms. This may explain the frequent paranoia, extreme agitation, and other psychotic symptoms in patients with PTSD as well. According to a large epidemiological study (Sareen et al., 2005), approximately half (52%) of PTSD patients experience a positive psychotic symptom at some point during their lifetime, which suggests a high incidence of psychotic symptoms in this population. Likewise, because of the broad psychotropic effects of AAs, these drugs are frequently prescribed for patients with PTSD that is comorbid with psychotic symptoms or behavioral disturbances (Bajor et al., 2011). However, contemporary evidence-based pharmacological treatment guidelines (American Psychiatric Association, 2004; Baldwin et al., 2005; Bandelow et al., 2012; Canadian Psychiatric Association, 2006) suggest that AAs should be carefully considered only after assessing the risk/benefit ratio when concomitant psychotic symptoms are present or when first-line approaches are ineffective in controlling PTSD symptoms. Accordingly, the cautious use of AAs for PTSD patients is warranted based on the acceptability issues and high dropout rates due to AEs reported in a recent meta-analysis and the intolerability of ziprasidone in an RCT that was terminated early for the treatment of PTSD (Kellner et al., 2010).

Based on the results of the present meta-analysis and meta-regression, AAs appear to be effective for the control of global PTSD symptoms regardless of the administration method (monotherapy or add-on therapy). Current research has primarily investigated AAs as an add-on therapy concomitant with ongoing antidepressant treatments; there is a paucity of RCT data regarding

AA monotherapy for PTSD. In fact, only one RCT included in the present meta-analysis reported a clear beneficial effect of risperidone compared to placebo among the three monotherapy RCTs evaluated. Therefore, it is not possible to conclude whether monotherapy or add-on treatment with AAs is more effective.

The type of trauma may also influence treatment effects in patients with PTSD (Martenyi et al., 2002). Cumulative childhood physical or sexual trauma was found to be significantly and negatively correlated with the response to paroxetine treatment (Marshall et al., 1998), and a placebo response was highly correlated with a history of past sexual trauma (Connor et al., 2001). To date, no RCTs investigating AAs for PTSD have identified such a trend. However, the meta-regression analysis of avoidance in the present study demonstrated a moderator effect of trauma type, wherein civilian trauma patients may be more responsive to AA add-on therapy than patients with combat trauma. Clearly, this effect needs to be replicated and supported by further RCTs to determine whether it is due to chance.

The present meta-analysis included five RCTs for the evaluation of the effects of AAs on depression (Bartzokis et al., 2005; Carey et al., 2012; Krystal et al., 2011; Rothbaum et al., 2008; Stein et al., 2002). There was a greater improvement in depression in these studies, as evidenced by a SMD of −0.524 which corresponds to a difference of −3.1 points on depression rating scales favoring AAs over placebo. This finding is in line with previous research and supports the efficacy of AAs for treating depression. In fact, quetiapine and aripiprazole were the first pharmacological agents to be officially approved as an add-on therapy for treating depression (Pae et al., 2011; Pae and Patkar, 2013; Pae et al., 2010). However, further research regarding this issue is required because quetiapine and aripiprazole were not included in the present meta-analysis. Furthermore, the present meta-regression revealed that AA monotherapy was more robust than AA add-on therapy, suggesting that chance effect was associated with the AA-mediated improvement of depression.

It has also been suggested that the duration of treatment may affect treatment outcomes (Marshall et al., 1998). However, no such effect was identified in the present meta-regression analyses of global PTSD symptoms. Here, only avoidance, which was more robust in short-term than in long-term trials, was influenced by the duration of treatment. It is possible that this was a chance effect, and so more data are required to evaluate this; no clinical data with which this result can be compared are available.

The likelihood of early dropouts for any reason or due to any type of AE was numerically higher in the AA group compared to the placebo group. This indirectly indicates tolerability issues in the AA group. However, only one study was terminated early due to this type of clinical issue (Kellner et al., 2010). Additionally, the fact that AEs following treatment with AAs are up to fourfold more prevalent in depression trials than in schizophrenia studies must be considered (Pae and Patkar, 2013; Pae et al., 2008b). In the present meta-analysis, weight gain was significantly greater in the AA group than in the placebo group (SMD = 1.1); this was particularly evident when evaluating olanzapine RCTs in which the SMD (1.1) exhibited a striking 2.5-fold increase (recalculated SMD = 2.7). This tolerability finding indicates that the use of AAs in PTSD patients should be weighed against the likelihood of various AEs, including extrapyramidal symptoms and metabolic complications (American Psychiatric Association, 2004; Baldwin et al., 2005; Bandelow et al., 2012; Canadian Psychiatric Association, 2006).

The present study had several limitations. First, the sample sizes of the individual studies included in the meta-analysis varied from 15 to 267 and a total of ~500 patients received either AAs or placebo. This small sample size is not sufficient to draw definitive conclusions regarding the current role of AAs in the treatment of PTSD even though the present meta-analysis was the largest of its type conducted to date. Indeed, only one study recruited more than a total of 250 patients for both treatment groups. Second, there was also a considerable difference between the observed SMDs in the mean change of the total score on the CAPS among the individual studies. This indicates hidden clinical heterogeneity among the studies due to the inclusion of different subjects (gender, trauma type, etc.) and variation in study characteristics (duration of treatment, diagnostic criteria, and structured interview, etc.). Third, the present meta-analysis included only published papers and the primary AAs evaluated were olanzapine and risperidone; this might limit the generalization of the results. Fourth, the durations of most of the trials were less than 12 weeks; this is an important issue because PTSD patients typically require long-term pharmacological treatment. Fifth, patient heterogeneity was not considered in the majority of studies. As noted above, AAs may be more appropriate for a subgroup of patients with predominantly psychotic-like features and future studies should focus on identification of more individualized treatments. Finally, although the use of effect sizes herein to compare treatments is generally considered to be superior to qualitative comparisons of different studies, this method has several limitations. The computation of effect sizes generally requires that the studies being compared should be of similar designs because this can influence the effect size. In particular, the comparison of effect sizes between substantially different studies should be performed cautiously because variation in study design can substantially influence the analysis of drug−placebo differences.

In conclusion, the evidence regarding the efficacy of AAs for the treatment of global and individual PTSD symptoms, particularly intrusion, is limited. The clinical relevance and importance of the present meta-analysis should be considered carefully during use of AAs in clinical practice.

Disclosures

The authors have reported no conflicts of interest.

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Contributors

Drs Pae and Han conceived and wrote the draft and also contributed to the final version of the manuscript. Drs. Lee and Wang contributed to data collection and their verification. Drs. Masand, Patkar and Serretti contributed to the critical comments and writing of the manuscript as well. All authors properly contributed to and finally approved the manuscript.

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