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Quetiapine Treatment for Post-Traumatic Stress Disorder: a Systematic Review of the Literature

Abstract

Paroxetine and Sertraline are the only medications approved in posttraumatic stress disorder (PTSD). However, about 60% of traumatized patients fail to show an adequate clinical response. Second generation antipsychotics are recommended as second-line monotherapy or third-line augmentation strategies and quetiapine appears as one of the most used and promising agents. Up to date, no reviews assessed the efficacy of quetiapine in the treatment of PTSD. We aimed to assess the effectiveness and general safety of quetiapine on PTSD. A systematic review was conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and Cochrane guidelines, selecting studies that evaluated the efficacy of quetiapine on global or specific PTSD symptomatology. Ten studies (n = 894) were considered eligible for qualitative synthesis: one case report, one case series, one prospective cohort study, 3 open-label trials, 3 retrospective studies, one RCT. Quetiapine was effective on global PTSD symptomatology assessed in 6 studies as well as on re-experiencing (4/4 studies), avoidance (4/3 studies) and hyperarousal (4/4 studies), flashbacks (2/2 studies), depressive (4/4 studies), anxiety (1/1 studies), psychotic (3/3 studies), insomnia (4/5 studies), nightmares (3/3 studies) specific symptoms and PTSD domains. Sedation was among the most frequently observed adverse effects and the main cause of drug discontinuation. Preliminary findings support the efficacy of quetiapine in ameliorating symptoms relative to PTSD and its overall safety. However, quetiapine use in PTSD cannot be recommended yet as studies mainly rely on open-label, retrospective studies or case series.

Key words: PTSD, Drug Resistance, Quetiapine, Pharmacotherapy.

Introduction

Posttraumatic stress disorder (PTSD) is a common mental disorder consequence of exposure to traumatic events. Its symptoms consist of 4 major diagnostic clusters: intrusion/re-experiencing symptoms, avoidance symptoms, negative cognitions, symptoms of hyperarousal [1,2]. Psychotherapy and pharmacotherapy recommendations differ across PTSD treatment guidelines. In a recent systematic review of 14 guidelines, all of them recommend cognitive behavior therapy (CBT) as a first-line psychological treatment while 6 guidelines recommend Eye Movement Desensitization and Reprocessing (EMDR) therapy. Thirteen guidelines recommend an selective serotonin reuptake inhibitors (SSRI) as first-line pharmacological option for PTSD and 10 include venlafaxine as a first-line pharmacological treatment option [3]. However, SSRIs are associated with an overall response rate of ≈ 60% and only ≈ 25% of patients achieve a complete remission [4]. For this reason, several studies evaluated the efficacy of alternative and combination treatments to enhance the therapeutic response [5]. For instance, some guidelines recommend antipsychotics as second-line monotherapy or third-line augmentation strategies, others recommend avoiding their use [6]; however, quetiapine appears to be one of the more promising, investigated and likely more used agents in PTSD. From 1999 to 2018, quetiapine remained the most commonly prescribed antipsychotic in Veterans Health Administration care [7-9]. This primacy is confirmed also by large sample studies on traumatized civilians in which quetiapine prescription rate achieved 25-30 % [10,11]. Although off-label quetiapine is widely prescribed in clinical practice and its efficacy in treating PTSD symptoms has been described, to the best of our knowledge no systematic collection of the available findings has yet supported or disconfirmed clinical recommendations [6]. The aim of our study is hence to evaluate the efficacy of quetiapine in the treatment of PTSD through a systematic review of

the literature. As a secondary outcome, reports concerning adverse effects of quetiapine in the selected studies will be collected and discussed.

Material and Methods

We conducted a systematic review of the literature available between 1998 and 22 February 2022. PubMed and Web of Science (all databases) were searched using the following search builder: (quetiapine AND (PTSD or posttrauma* or trauma* or combat or stress)). Population, Intervention, Comparison, Outcomes and Study (PICOS) design criteria [12] for study selection were applied and are reported in Table 1. Articles not in English were excluded. Due to heterogeneous designs of the available studies and the complex clinical phenomenology of this mental disorder, we also included non-RCT studies to better report on a broader field of research. A total of 680 (437 Web of Science, 243 PubMed) items were retrieved from the search databases and reference cross-check. Duplicates (189) were removed. The remaining studies were independently evaluated by 2 reviewers (C.C. and C.A.) and included or excluded after reaching a final consensus. Quality of studies was evaluated by means of AMSTAR 2 scores, a 16-item assessment tool to check the quality of a systematic review: High (No or one non-critical weakness), Moderate (More than one non-critical weakness), Low (One critical flaw with or without non-critical weaknesses), Critically low (More than one critical flaw with or without non-critical weaknesses) [13]. Figure 1 reports the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart regarding the different phases of this review [14]. (Table 1 and Figure 1, about here).

Results

- **Effectiveness**

Ten studies (n = 894) with different designs and population (7 military and 3 civilian samples) were included in this systematic review (Table 2). In a case report of a 49-year-old patient with resistant PTSD, the addition of modest dosage of quetiapine to 40 mg/d of paroxetine resulted in the improvement of PTSD symptoms [15]. In a case series of 5 patients (civilian; 60% male; mean duration treatment "not available") the addition of quetiapine 150-200 mg/d to a stable SSRI/SNRI and gabapentin combination therapy markedly reduced persistent flashbacks [16]. In an open-label trial (n = 20 veterans; 95% male; mean age of 53 years; mean duration treatment of 6 weeks; "Moderate" quality according to the AMSTAR 2 tool), the addition of quetiapine 25-300 mg/d to a psychotropic medication (except antipsychotics and at constant dose for at least 1 month before baseline visit) provided a significant improvement on global PTSD severity by week 2, and specifically on re-experiencing domains as well on insomnia, depression, and negative/positive psychotic symptoms [17]. In another open-label trial (n = 15 civilians; 100% male; mean age of 49 years, mean duration treatment of 8 weeks; "Moderate" quality according to the AMSTAR 2 tool) the addition of quetiapine 100–400 mg/d to a stable SSRI therapy provided a significant improvement on global PTSD severity and on re-experiencing, hyperarousal and avoidance domains, depression and insomnia [18]. In a prospective cohort study (n = 270 veterans, 97% male; mean age of 53,7 years; "Low" quality according to the AMSTAR 2 tool) the addition of quetiapine 25-600 mg/d or prazosin 1-25 mg/d to a psychotropic medication for treating nighttime symptoms was evaluated as measured by continued therapy for 0-6 months and 3-6 years. While short-term effectiveness was comparable, patients in the quetiapine group were significantly more likely to discontinue long-term therapy to the study end date (48.4% versus 24%) due to adverse effects or ineffectiveness [19]. In a retrospective study (n = 327 veterans,

95% male; mean age of 53.7 years; mean duration treatment of 4 years; "Low" quality according to the AMSTAR 2 tool) the efficacy of various medications used to treat nightmares was evaluated. The three most prescribed agents as monotherapy were: prazosin 32.4%, risperidone 24.7% and quetiapine 22%. Efficacy was determined using three levels of response (absent, partial and full response). Quetiapine administered at a dosing range of 12.5–800 mg/d obtained a success rate of 50% while prazosin and risperidone had a success rate of 49% and 77% respectively [20]. In an open-label trial quetiapine monotherapy 25–400 mg/d (n = 53 veterans, 100% male; mean age of 55 years; mean duration treatment of 6 weeks; "Moderate" quality according to the AMSTAR 2 tool) provided a significant improvement on global PTSD symptoms severity, on re-experiencing, avoidance and hyperarousal domains and on negative and positive psychotic symptoms [21]. In a retrospective study the addition of quetiapine 25-700 mg/d was evaluated in 68 resistant veterans with PTSD (100% male; mean age of 55 years; mean duration treatment of 25 weeks; "Moderate" quality according to the AMSTAR 2 tool), 74% of patients were judged much or very much improved in at least one refractory symptom of PTSD: re-experiencing, avoidance/numbing, arousal, sleep disturbance, nightmares, depressed mood, flashbacks [22]. The only RCT (n = 80 veterans, 100% male; mean age of 53 years; mean duration treatment of 12 weeks; "Moderate" quality according to the AMSTAR 2 tool) conducted on quetiapine in PTSD demonstrated that quetiapine monotherapy 50–800 mg/d was more effective than placebo on global PTSD symptoms severity and on re-experiencing and hyperarousal domains as well on anxiety, depression, and positive psychotic symptoms, but not on the avoidance/numbing domains and insomnia [23]. In an observational retrospective study of 50 resistant PTSD veterans (96% male; mean duration treatment of 10-12 weeks; "Low" quality according to the AMSTAR 2 tool) and declined trauma-focused therapy, 21 over 24 patients taking quetiapine 50–400 mg/d and 0 over 11 taking either risperidone (1-4 mg/d) or valproate (500–2000 mg/d) monotherapy,

were engaged in treatment and completed it. Quetiapine was also associated to greater improvements in sleep interruptions and nightmares [24]. Regarding concomitant psychotherapy, initiation or change in psychotherapy within 3 months of randomization was an exclusion criterion in Villareal et al. [23], need for concurrent psychotherapy was an exclusion criterion in Pivac and Kozarić-Kovacić [21]. No concomitant psychotherapy was provided in Filteau et al. [16], Hamner et al. [17], Ahearn et al. [18], Byers et al. [19], Detweiler et al. [20], Sokolski et al. [22]. In Sattar et al., the patient that at first declined group therapy was engaged in psychosocial treatment 3 days after quetiapine initiation [15].

- **Reported Adverse Effects**

No adverse effects were reported in Sattar et al. [15] and this topic was not evaluated in Filteau et al. [16], Ahearn et al. [18] and Detweiler et al. [20]. In Hamner et al. [17] the most common adverse effects reported were sedation (37%), dizziness and dry mouth (16%), hypersalivation, diarrhea, headache and amblyopia (5.3%), without significant changes in weight, vital sign measurements, or neurologic ratings. In Byers et al. [19] sedation and metabolic effects occurred more frequently in the quetiapine group (21% and 9.1% respectively) than in the prazosin group (1.6% and 0% respectively). Discontinuation rate was higher in the quetiapine group compared to prazosin group due to adverse effects, especially sedation (34.9% vs 17.7%) In Pivac and Kozarić-Kovacić [21] side effects were not evaluated, although a post hoc study sharing the same sample reported the following side effects frequency: hypotension (50.9 %), sedation (39.6%), anticholinergic effect (9.4%) and weight gain (9.4%) [25]. In Sokolski et al. [22] the side effects reported were: asthenia (13.6%), at least one among nausea, dizziness, dry mouth, muscle twitching or weight gain (0.68%); four patients (5.9%) discontinued quetiapine due to excessive sedation. In Villareal et al. [23] the

side effects in the quetiapine group were dry mouth (15.8%), somnolence (13.4%), and sedation (7.4%). Nine patients (11.2%) in the quetiapine and three (3.7%) in the placebo group dropped out because of adverse effects. No significant differences in weight, pulse, or blood pressure measurements occurred between quetiapine and placebo. In Baig et al. [24], the frequency of side effects was not reported although in the risperidone and valproate groups were observed more daytime sedative effects compared to quetiapine group. (Table 2, about here).

Discussion

PTSD symptoms make the treatment of this disorder particularly challenging. In addition, different subtypes have been characterized (reexperiencing/hyperaroused, externalizing, internalizing, dissociative, psychotic, high-symptom, combat and noncombat-related subtypes) and are related to different history of disease and prognosis [26-31]. Additionally, several putative factors contributing to SSRI resistance were reported: severity of illness, previous multiple and/or combat traumas, chronicity of illness, male sex, comorbidities [5] and sleep disturbances appear the most associated to refractory symptoms [23]. Despite this and its high heterogeneous clinical presentation, the only medications approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for PTSD are sertraline and paroxetine [32] although other drugs reported significant evidence in the treatment of PTSD [33,34]. The first case report describing use of quetiapine in a patient with PTSD is reported by Sattar and colleagues [15]. In this report as well as in Filteau et al. [16], Hamner et al. [17], Ahearn et al. [18], Sokolski et al. [22], Byers et al. [19], quetiapine was evaluated as augmenting agent (≈ 50% of the whole sample) while in other studies it was evaluated as monotherapy agent [20,21,23,24]. In two studies a comorbidity with major depressive

disorder may be present [19,23]. Global PTSD symptomatology was assessed only in 6 articles [15,17,18,21,22,23] where quetiapine provided a beneficial effect. In four studies quetiapine was effective on specific symptoms and PTSD domains [16,19,20,24]. Nightmares were evaluated in three studies, quetiapine was effective and in two of them comparable or inferior to prazosin [19,20,22]. Quetiapine was effective on re-experiencing, avoidance and hyperarousal domains in three studies [18,21,22] while in one study, the single RCT available [23], quetiapine was also effective on re-experiencing and hyperarousal domains but not on avoidance. Insomnia was evaluated in five studies and quetiapine was effective in all studies [17,18,22,24] except one [23]. Of note, in a post hoc analysis of the latter study [23] quetiapine was effective on insomnia by week 2 [35]. Quetiapine was effective on flashbacks, evaluated in two studies [16, 22] and in anxiety, evaluated in one study [23]. Quetiapine was also effective on depressive and psychotic symptoms in all the studies that evaluated them [17,18,21,22,23]. The dose of quetiapine across studies encomprises the whole dose range (25-800 mg/d). However, dose mean values - provided by five studies - are generally low and range from 100 to 258 mg/d, suggesting that quetiapine may be effective on symptoms even at low/moderate dosages (Table 2). Sedation was the most reported adverse effect: it occurred more frequently in the quetiapine group than the prazosin group [19] and less frequently than valproate and risperidone [24]. The pharmacological mechanism by which quetiapine may ameliorate PTSD symptoms is undefined. Quetiapine is a multifunctional, second-generation antipsychotic, a thienobenzodiazepine derivative. It is approved by the FDA for the treatment of schizophrenia and bipolar disorder in adult patients, but it has shown to be effective in other conditions such as anxiety disorders, dementia, and delirium. It is a characterized by antagonism for D2, H1, 5-HT2A, 5-HT2C, α1 receptors while norquetiapine - its main metabolite - is a norepinephrine reuptake transporter inhibitor and characterized by antagonism for the H1, 5-HT1A, 5-HT1E, 5-HT2A, 5-HT2B, 5-HT7, α1, M1, M3, M5

receptors (Figure 2) [36,37]. The D1/H1/5HT2A/5HT2C/α1 antagonist activity, underling its sedative and anxiolytic properties, may contribute to i) ameliorate nightmares/sleep disturbances and hyperarousal [37-43] although its anti-arousal effects appears to be direct and unrelated to psychosedation [24] ii) help re-socialization (decreasing levels of anxiety) and improve therapeutic alliance like oxytocin promotes socially-oriented behaviors (normalizing amygdalar and insular activity) [24,44-45] (Figure 2). The anti-D2/5-HT2A activity of quetiapine may contribute to treatment of trauma-related intrusive thoughts, flashbacks, and psychotic symptoms [16,17,18,21,22,36]. Included studies reported that quetiapine might be an effective and safe pharmacological tool improving a wide range of psychiatric symptoms relative to PTSD. (Figure 2, about here)

Limitations

This study is not without limitations. Data available were derived mainly from non-RCT trials and, as a potential confounding factor, less than 3 % of the patients included in this review were civilians or females. Therefore, the strength of the evidence is too weak to recommend quetiapine in PTSD and more randomized controlled studies are needed. Such studies would enroll patients characterized by specific clinical features that have been linked to inhibitor serotonin transporter (SRI) resistance. Furthermore, it may be useful to know and recognize which PTSD sub-phenotypes may specifically benefit from a treatment with quetiapine (as monotherapy or additional therapy to SRI) to develop more effective treatment strategies. Finally, other atypical antipsychotics with a different receptor profile are reported as reasonable therapy option in patients with PTSD (such as aripiprazole that has a very low affinity toward M1 and H1 recptors), leaving open questions on how the major neurobiological pathways related to PTSD are affected by different antipsychotics [46,47].

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Authors Contributions

Conceptualization: C.C. Supervision: C.A. Writing-original draft: C.C. Writing review & Editing: I.C., S.D.

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Table 1. PICOS criteria for study selection

Parameter	Inclusion	Exclusion
Patients	Diagnosis of PTSD; Age ≥18 years	Presence of psychiatric comorbidities except major depressive disorder
Intervention	Quetiapine, any dose as monotherapy or augmenting agent (sequential therapy)	Initial combination therapy including quetiapine and other drugs
Comparator	None or placebo or other active treatments	
Outcomes	Quantitative or qualitative evaluation of overall or specific symptoms of PTSD	
Study design	Case reports, case series, retrospective, prospective, cohort, cross sectional studies, randomized and non-randomized controlled trial	Reviews, expert opinion, comments, conference report, post-hoc studies, study published in any other language than English

Table 2. Descriptive comparison between studies considered

Source	Study Design Add-on or Monotherapy	Sample and Gender (civilians or veterans)	Range (and mean dose) (mg/d)	Duration	Effectiveness - changes from baseline assessment scores	AMSTAR2
Sattar et al., 2002	Case report Add-on to paroxetine	1 (100% male) (civilian)	150	12 months	QTP associated with marked improvements in HAM-D and CAPS scores	NA
Filteau et al., 2003	Case series Add-on to SRI and GBP	5 (60% male) (civilians)	150-200	NA	NA	NA
Hamner et al., 2003	Open-label trial Add-on to psychotropic medication (SRI, anticonvulsants, sleep agents)	20 (95% male) (veterans)	25-300 (100 ± 70)	6 weeks	QTP associated with significant improvements in HAM-D, PANSS and CAPS scores	Moderate
Ahearn et al., 2006	Open-label trial Add-on to SSRI	15 (53% male) (civilians)	100–400 (216)	8 weeks	QTP associated with significant improvement in HAM-D, CGI-I/S, PSQI, CAPS scores	Moderate
Byers et al., 2010	Prospective cohort study Add-on to SSRI, sleep agents	270 (97% male) (veterans)	QTP 25-600 PRZ 1-25	≤ 6 months 3 – 6 years	NA	Low
Detweiler et al., 2016	Retrospective study Monotherapy	327 (95% male) (veterans)	QTP 12.5–800 PRZ 1–20 RIS 0.25–6.0	4 years	NA	Low
Pivac & Kozarić-Kovacić, 2006	Open-label trial Monotherapy	53 (100% male) (veterans)	25–400	6 weeks	QTP associated with significant improvement in PANS, CGI-S, CAPS scores	Moderate
Sokolski et al., 2003	Retrospective study Add-on to SRI, anticonvulsants, antipsychotics	68 (100% male) (veterans)	25-700 (155 ± 130)	25 weeks	QTP associated with a marked improvement in CGI-I scores	Moderate
Villareal et al., 2016	Randomized, double-blind, placebo-controlled trial Monotherapy	80 (100% male) (veterans)	50–800 (258)	12 weeks	QTP superior to PLC for CGI-S/I, PANSS, HAM-A, HAM-D, CAPS	Moderate

Baig et al., 2019	Retrospective study Add-on to SRI, mood stabilizers, sleep agents	50 (96% male) (veterans)	QTP 50–400 (180) VPA 500–2000 (1625) RIS 1–4 (2)	10-12 weeks	NA	Low
QTP, quetiapine; HAM-D, Hamilton Depression Rating Scale; CAPS, Clinician Administered PTSD Scale; SRI, serotonin reuptake inhibitor; PANSS, Positive and Negative Syndrome Scale; CGI-I/S, Clinical Global Impression - Improvement/Severity; PSQI, Pittsburgh Sleep Quality Index; PRZ, prazosin; RIS, risperidone; NA, Not Available.						

Figure 1. PRISMA flowchart of information through the different phases of the review

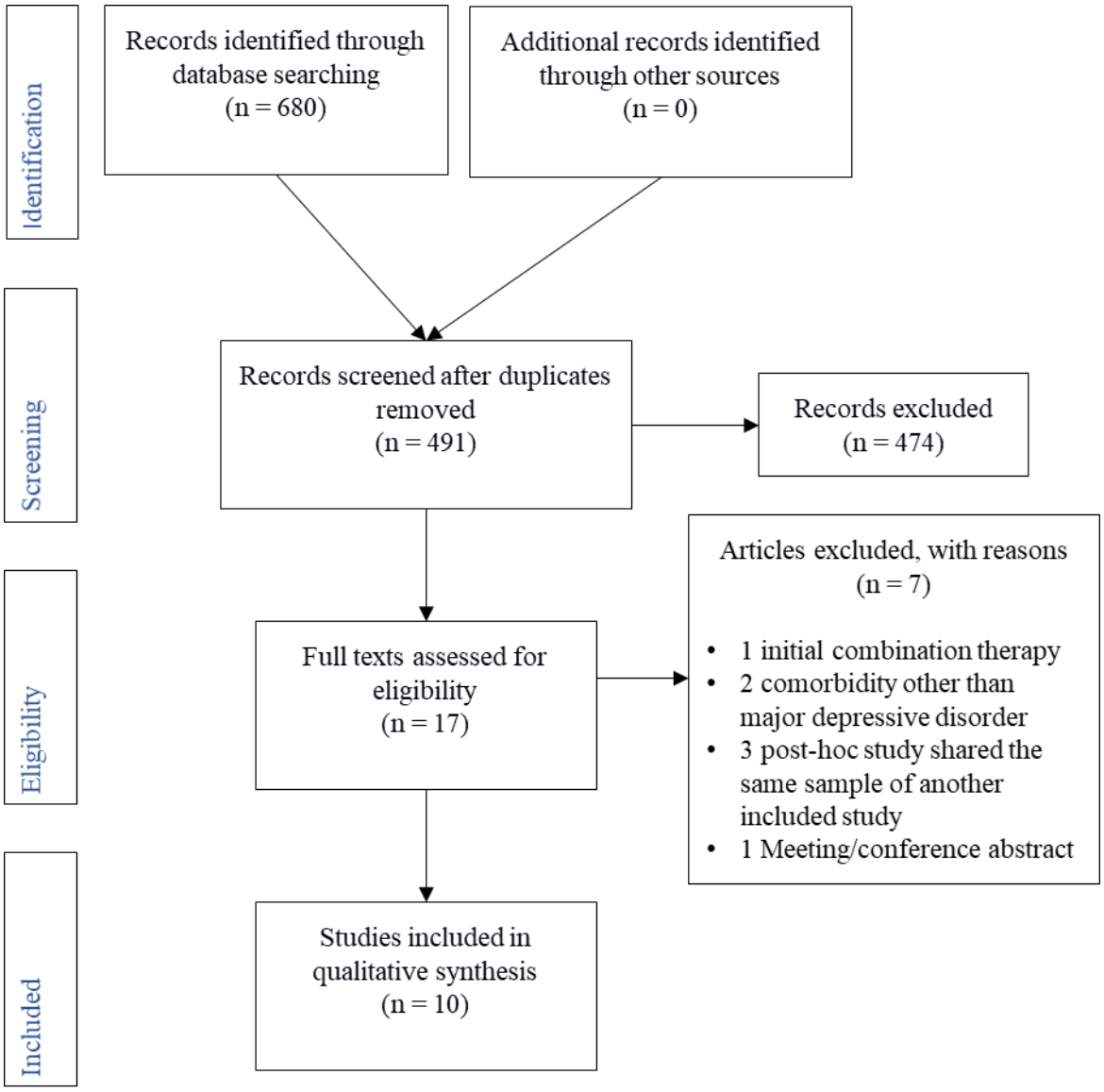
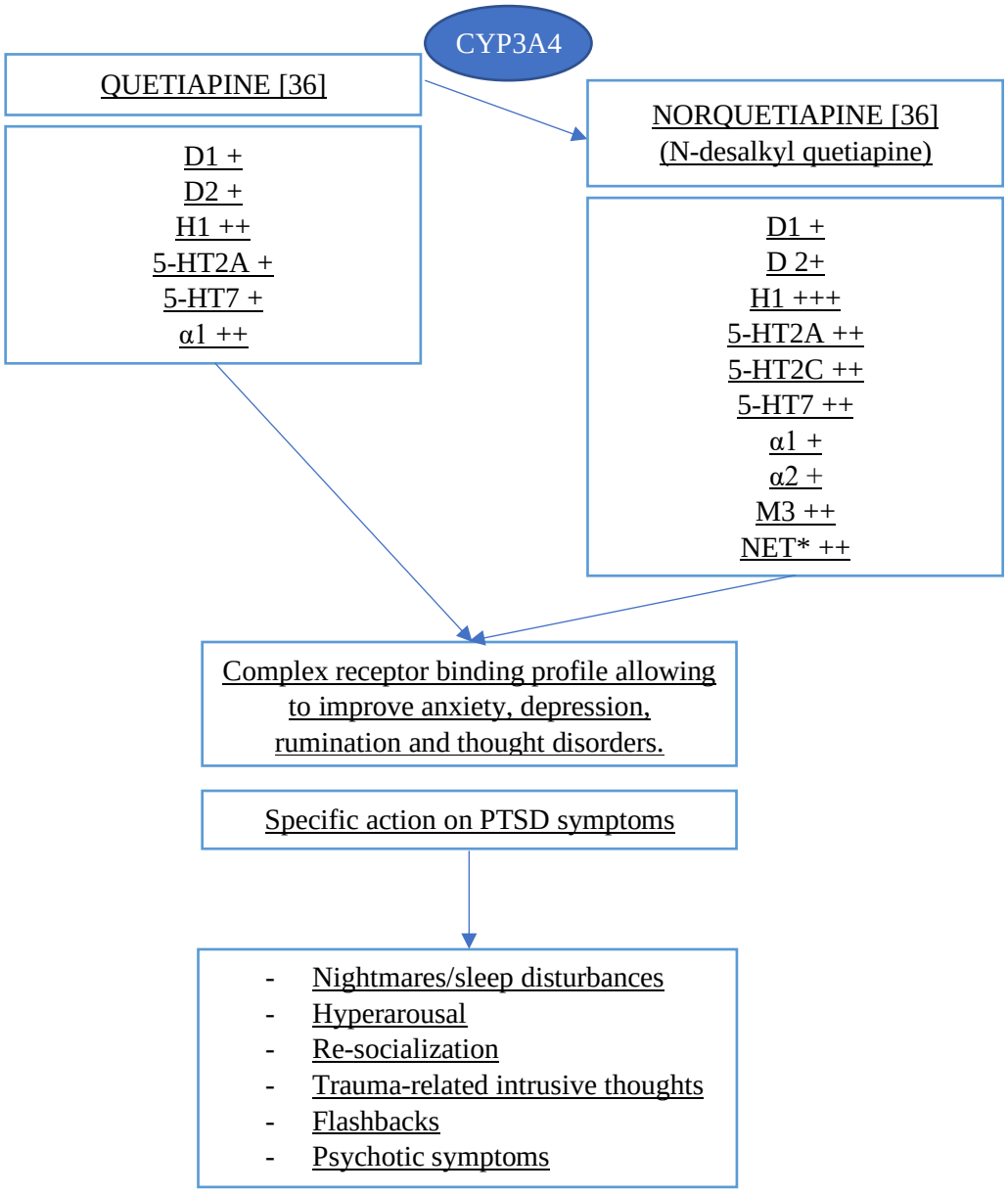


Figure 2. Potential mechanisms by which quetiapine could exert a positive impact in PTSD



***norepinephrine transporter**

+ Ki < 1000 nanomoles

++ Ki < 100 nanomoles

+++ Ki < 10 nanomoles