European Neuropsychopharmacology (2011) 21, 429–449

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REVIEW

Review of atypical antipsychotics in anxiety

Nienke C.C. Vulink[a,*], Martijn Figee[a], Damiaan Denys[a,b]

[a] *Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*
[b] *The Netherlands Institute for Neuroscience, an institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands*

Received 19 July 2010; received in revised form 30 November 2010; accepted 27 December 2010

KEYWORDS
Atypical antipsychotics;
Anxiety disorders;
Obsessive–compulsive disorder

Abstract

Atypical antipsychotics are increasingly used for treatment of anxiety disorders, either in mono- or combination therapy. This is the first review reporting on the use of atypical antipsychotics in monotherapy or augmentation in patients with primary anxiety disorders or anxiety (disorders) comorbid to schizophrenia, bipolar disorder (BPD) and major depressive disorder (MDD). We included 49 open-label trials, 32 randomized, placebo-controlled trials (RCTpls) and five randomized controlled trials without placebo arm with almost 6000 patients (open-label: 1710, randomized: 4145). An increasing number of RCTpls show promising results in 27–71% of patients with primary or comorbid anxiety disorders who were treated with monotherapy atypical antipsychotics or augmentation therapy. However, methodological flaws of included studies may limit conclusions of this review and larger placebo-controlled trials are warranted comparing standard treatment with monotherapy and augmentation therapy of atypical antipsychotics and placebo. In addition, higher dropout rates and side effects from treatment with atypical antipsychotics may limit the use of atypical antipsychotics in patients with anxiety disorders.

1. Introduction

The efficacy of atypical antipsychotics in schizophrenia and bipolar disorders has been well established. Lately, a growing number of trials report about the use of these atypical antipsychotics in anxiety disorders as well. Though promising results have been found both in mono- and combination therapy to antidepressants in patients with comorbid anxiety to schizophrenia, bipolar disorder (BPD) and major depressive disorder (MDD); the efficacy of atypical antipsychotics in anxiety disorders is not clear. A number of reviews on atypical antipsychotics in anxiety disorders has been published (Brooke et al., 2005; Fountoulakis et al., 2004; Gao et al., 2006; Jeste and Dolder, 2004; Nemeroff, 2005), however, these mainly contain case reports and open-label trials. In view of the increasing number of randomized controlled trials with or without placebo arm published recently, we here aim to summarize in a narrative review the current knowledge of the efficacy and tolerability of atypical

* Corresponding author. Department of Psychiatry, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands. Tel.: +31 20 8913602; fax: +31 20 8913701.
E-mail address: n.c.vulink@amc.nl (N.C.C. Vulink).

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doi:10.1016/j.euroneuro.2010.12.007

antipsychotics in monotherapy and combination therapy in patients with primary and comorbid anxiety disorders.

2. Experimental procedures

English-language literature cited in MEDLINE, PsychINFO (1967–2010), Embase (1974–2010) was searched for open-label trials and (double-blind) randomized controlled trials using the following keywords: quetiapine, olanzapine, risperidone, aripiprazole, ziprasidone, clozapine, atypical antipsychotic, anxiety, and the DSM-IV diagnoses of obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), panic disorder (PD), agoraphobia, and generalized anxiety disorder (GAD). Search results were limited to open-label trials and RCTs of adult patients. In addition, open-label trials and (double-blind) randomized controlled trials of comorbid anxiety (disorders) in patients with primary diagnoses of schizophrenia, bipolar disorder (BPD) and major depressive disorder (MDD) have been included in our review. Furthermore, we used a trial result register (Clinicaltrial.gov) to include all possible medication trials with atypical antipsychotics in anxiety disorders.

We divided the selected trials in: (1) monotherapy and augmentation therapy of atypical antipsychotics in patients with primary diagnoses of schizophrenia, bipolar disorder (BPD), major depressive disorder (MDD) and comorbid anxiety (disorders); (2) monotherapy of atypical antipsychotics in primary anxiety disorders; (3) augmentation therapy of atypical antipsychotics in primary anxiety disorders. In addition, we categorized trials based on design: (1) open-label trials, (2) randomized controlled trials without placebo arm (RCT) and (3) double-blind, randomized, placebo-controlled trials (RCTpl) and we summarize mean changes on similar questionnaires used per diagnosis and response rates of included trials in relation to the design of the study. Conclusions of the efficacy of atypical antipsychotics on anxiety (disorders) and OCD were only based on trials using an anxiety questionnaire or the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) to score severity of anxiety or OCD symptoms and conclusions were categorized in relation to the design of the included studies. In order to compare the proportion of completers in every RCTpl, we used a Mann–Whitney U test. All tests were 2-tailed and an α-level of 0.05 was used to determine statistical significance. Data were analyzed with the Statistical Packaged for Social Sciences version 14.0 SPSS Inc. Chicago, III.

3. Results

Our search yielded 49 open-label trials, 32 RCTs including a placebo arm (RCTpl), four RCTs without placebo arm (RCT) and one double-blind crossover study including 5855 patients with anxiety disorders. First, we found ten open-label trials, and six RCTpls of both monotherapy and augmentation therapy of atypical antipsychotics in patients with primary diagnoses of schizophrenia, bipolar disorder (BPD), major depressive disorder (MDD) and comorbid anxiety (disorders) (Table 1). In addition, we found twelve open-label trials, eight RCTpls, one double-blind crossover study and one RCTs of monotherapy of atypical antipsychotics in primary anxiety disorders (Table 2). Finally, 27 open-label trials, 18 RCTpls and three RCTs of augmentation therapy of atypical antipsychotics in anxiety disorders were identified (Table 3).

Three additional completed RCTpls were found in the Clinicaltrial.gov trial register (ziprasidone in social anxiety disorder and PTSD, and risperidone in GAD), though no published results were found and principal investigators did not respond to our invitation to include their results in our review. The study of risperidone in patients with GAD included a synopsis summarizing overall negative results.

3.1. Schizophrenia/schizoaffective disorder

Five open-label studies, and two RCTpls reported on the efficacy of monotherapy of atypical antipsychotics in patients with comorbid anxiety or obsessive–compulsive symptoms to schizophrenia or schizoaffective disorders (Table 1) (Kasper, 2004; Blin et al., 1996; Tollefson et al., 1998; Buckley et al., 2004; Littrell et al., 2003; Stern et al., 2009; Glick et al., 2008).

Three open-label studies did not use anxiety questionnaires, while in one open-label study the Liebowitz Social Anxiety Scale (LSAS) was used to score social anxiety and in another open-label study the Y-BOCS was used. Stern et al. (2009) showed that aripiprazole significantly decreased social anxiety (25%) in patients with schizophrenia during 8 weeks of treatment, but after 10 months no significant improvement was still present. Glick et al. (2008) showed that aripiprazole improved Y-BOCS scores (52%) in patients with OCD and schizophrenia and they defined response criteria (decrease Y-BOCS $\geq$ 35% or CGI-I $\leq$ 2) with 40% responders. Both RCTpls did not use an anxiety questionnaire.

3.2. BPD

In line with results in patients with schizophrenia, results in patients with BPD and comorbid anxiety are similar as is illustrated by one RCTpl of monotherapy and one RCTpl of both monotherapy as well as augmentation of atypical antipsychotics that both showed significant mean decreases of the Hamilton Rating Scale for Anxiety (HAM-A) of 53–70% compared to 48% in patients treated with placebo (Table 1) (Hirschfeld et al. 2006; Tohen et al., 2007). However, in another RCTpl no significant decrease of HAM-A scores was reported (Sheehan et al., 2009). Only Tohen et al. (2007) defined response as a decrease of the HAM-A $\geq$50%, though the number of responders was not reported. The authors stated that the likelihood of achieving HAM-A remission (HAM-A total score $\leq$7 at endpoint) was significantly greater in patients receiving olanzapine relative to those receiving placebo (RR: 2.32; NNT: 7,58). Another arm in the same RCTpl showed that augmentation of olanzapine to fluoxetine significantly increased the likelihood of achieving HAM-A response compared to placebo (RR: 2.00; NNT: 3.33) or compared to olanzapine monotherapy (RR: 1.69; NNT: 4.08) (Tohen et al., 2007). In one open-label study of aripiprazole in patients with BPD and OCD, a significant decrease of Y-BOCS scores of 57% was reported, but no response criteria were used (Uguz, 2010).

3.3. MDD

Finally, similar positive results were found in four open-label studies, and one RCTpl on the augmentation of atypical antipsychotics in patients with primary MDD and comorbid anxiety disorders (Table 1). Mean HAM-A scores decreased 67–80% in the open studies (Adson et al., 2004; Adson et al., 2005; McIntyre et al., 2007; Targum and Abbott, 2000; Yargic LI, 2004). None of the open studies defined response criteria. A mean reduction of the HAM-A of 55% was reported in a RCTpl in

Table 1 Atypical antipsychotics in primary schizophrenia, bipolar disorder or major depressive disorder with comorbid anxiety disorders (n=16).

Indication Medication Mono or Aug	TR or naive	Author	Year of publ.	N	Mean dose [SD] or range (mg/d)	Design	Trial length (weeks)	Decrease on questionnaire (%)	p	Completer/ ITT/LOCF analysis	Completers N (%)	Response criteria; responders N (%)
Schizophrenia/schizoaffective disorder with comorbid anxiety (disorders)												
Quetiapine Mono	TR	Kasper	2004	415	432	Open	156	BPRS Factor I [a] mean (95% CI): 6 weeks: −1.13 (50) 156 weeks: −1.33 (34)	–	?	382 (92)	*No response criteria*
Risperidone Mono	TR	Blin	1996	21 [b]	7.4	Open	4	PAS 34.1 (57) PANNS 44.7 (36) BPRS 25.8 (37) CGI 2.3 (50)	<0.05 <0.05 <0.05 <0.05	ITT/LOCF	17 (81)	Decrease PANNS ≥ 20%; 17 (81) or decrease BPRS ≥ 20%; 18 (86)
Olanzapine Mono	TR	Tollefson	1998	335 [c]	Olanzapine: low 6.6 (1.4) medium 11.6 (1.5) high 16.3 (1.6) haloperidol: 16.4 (4)	RCTpl	6	BPRS Factor I [a]: ol low: 1.1 (13) ol medium: 3.4 (38) ol high: 3.5 (36) vs pl 1.4 (16) and haloperidol 3 (31)	ns p=0.042 p=0.046 ns	ITT/LOCF	263 (74) (no distinction between treatment groups)	*No response criteria*
Quetiapine Mono	TR	Buckley	2004	426	150–750	RCTpl	6	BPRS item anxiety ?	<0.001	?	Completers: ? (96) que vs ?(97) pl	*No response criteria*
Risperidone Mono	?	Littrell	2003	24	17 (4.3)	Open	26	PANNS (total score) 28.3 (34) PANNS (anxiety items) 2.2 (52)	=0.0003 <0.0001	?	?	*No response criteria*
Aripiprazole Mono	?	Stern	2009	16–10 [d]	26 (6.8)	Open	8 weeks + 10 months	Short-term: LSAS 18.8 (25) SDS 11.9 (72) QOL 1 (53) Extension phase: LSAS 11 (24) SDS +0.7 (15) QOL 0.1 (3)	p=0.013 p=0.001 p=0.001 ns ns ns	ITT/ LOCF	Completers short-term 14 (88); extension phase 7 (70)	*No response criteria*
Schizophrenia with comorbid OC symptoms												
Aripiprazole Mono	Naive	Glick	2008	11	Mono: 10–30	Open	6	Y-BOCS 13 (52) CGI-S 1.1 (27) CGI-I 2.3		Completers	7 (64)	Decrease Y-BOCS ≥ 35% or CGI-I 1 or 2 6 (40)

(continued on next page)

Table 1 (*continued*)

Indication Medication Mono or Aug	TR or naive	Author	Year of publ.	N	Mean dose [SD] or range (mg/d)	Design	Trial length (weeks)	Decrease on questionnaire (%)	p	Completer/ ITT/LOCF analysis	Completers N (%)	Response criteria; responders N (%)
Bipolar disorder with comorbid anxiety (disorders)												
Quetiapine Mono	TR	Hirschfeld	2006	539[e]	300 or 600	RCTpl	8	HAM-A Q300 9.9 (53%) HAM-A Q600 10.8 (58%)	<0.001 <0.001	?	que 300: 121 (69) que 600: 98 (54) pl: 107 (59)	*No response criteria*
Olanzapine Mono + Aug	?	Tohen	2007	359[f]	Mono: 9.9 Aug: 7.7 ol and 41.1 fluo	RCTpl	8	Mono: HAM-A 15 (67) ol vs 11 (48) pl Aug: HAM-A 16.6 (70) ol vs 11 (48) pl	=0.002 =0.002	?	Mono: 71 (42) ol vs 60 (38) pl Aug: 19 (61) ol vs 60 (38) pl	Decrease HAM-A ≥ 50%; The likelihood of achieving HAM-A response was two times greater in patients receiving olanzapine–fluoxetine combination relative to those receiving placebo (RR: 2.00; NNT: 3.33) or 1.7 times greater compared to olanzapine monotherapy.
Risperidone Mono	TR + naïve	Sheehan	2009	111	2.5 (1.1; 0.5–4)	RCTpl	8	HAM-A ? (graph only) CGI-21 Anxiety ? (graph only)	ns ns	ITT/LOCF	27 (55) risp vs 36 (68) pl	50% endpoint improvement on efficacy parameters? (graph only) ns
Bipolar disorder with comorbid obsessive–compulsive disorder												
Aripiprazole Mono	Naive	Uguz	2010	3	15–25	Open	8	Y-BOCS 17 (57)	na	na	na	na
Major depressive disorder with comorbid anxiety disorders												
Quetiapine Aug	TR	Adson	2004	11	180	Open	9	HAM-A 19 (76) HAM-D 15 (72) SAI 21 (41)	<0.0001 <0.0001 <0.001	ITT/LOCF	10 (91)	?
Quetiapine Aug	TR	Targum	2005	21	105	Open	?	HAM-A 17 (67) HAM-D 7 (48)	<0.001 <0.001	?	?	?
Quetiapine Aug	TR	Yargic	2004	120	?	Open	?	?	?	?	?	*No response criteria*
Quetiapine Aug	TR	McIntyre	2007	58	182 [69] (200–600)	RCTpl	8	HAM-A 12.5 (55) que vs 5.9 (26) pl	= 0.002	ITT	18/29 (62) ol vs 16/29 (55) pl	Decrease HAM-A ≥ 50%: 62% (n?) vs 28% (n?) (p = 0.02)
Aripiprazole Aug	TR	Adson	2005	10	5–20	Open	9	HAM-A 20.6 (80) HAM-D 13,5 (59) and SDS 11.7 (64)	<0.001 <0.001 ? ?	ITT/LOCF	8 (80)	*No response criteria*

patients treated with quetiapine addition, compared to 26% in patients augmented with placebo. Furthermore, response was defined as a ≥50% decrease on the HAM-A and significantly more patients could be classified as responders in the quetiapine group compared to placebo (62% versus 28%) (McIntyre et al., 2007).

Taken together, atypical antipsychotics decreased mean scores of anxiety questionnaires with 24–80% in open-label studies in patients with secondary anxiety disorders comorbid to schizophrenia, BPD and MDD, while in RCTpls a mean decrease of 53–70% was reported in patients treated with atypical antipsychotics compared to 26–48% in patients treated with placebo. Only in one open-label study response was defined and 40% of patients could be classified as responders. Also one RCTpl defined response and 62% of patients treated with atypical antipsychotics could be classified as responders compared to 28% of patients treated with placebo. Three out of only four RCTpls that used an anxiety questionnaire in patients with BPD, MDD and secondary anxiety disorders showed significant decreases of anxiety symptoms compared to patients treated with placebo.

Most of the patients completed open-label trials (64–92%). No difference was found in mean proportion of patients with comorbid anxiety who completed their treatment of monotherapy or addition therapy of atypical antipsychotics (42–96%) in RCTpls compared to placebo (38–97%, $Z=-0.57$, $p>0.05$).

3.4. GAD

Generalized Anxiety Disorder (GAD), is an anxiety disorder characterized by chronic anxiety, exaggerated worry and tension, even when there is little or nothing to provoke it (DSM-IV, 1994). One open-label trial with olanzapine and one with ziprasidone showed a decrease of the HAM-A of 55–74% with a response rate (HAM-A decrease ≥50%) to ziprasidone of 54% in patients with GAD (Klieser et al., 2000; Snyderman et al., 2005).

One RCTpl with quetiapine showed a significant decrease of HAM-A scores of 52–60% compared to 45% in patients treated with placebo (Bandelow et al., 2010), with a significantly higher proportion of responders (63–71%) in patients treated with quetiapine 50 mg/d, 150 mg/d or paroxetine 20 mg/d compared to 52% of patients who responded to placebo. The other RCTpl however, did not show significant decreases of the HAM-A (Lohoff et al., 2010).

3.5. PTSD

PTSD is a common anxiety disorder that develops after exposure to a terrifying event or ordeal in which grave physical harm occurred or was threatened. Patients have symptoms related to re-experiencing the traumatic event, avoidance of stimuli associated with the trauma and numbing of general responsiveness and increased arousal (DSM-IV, 1994). Seven open-label studies and three RCTpls reported on the efficacy of monotherapy with atypical antipsychotics in patients with PTSD (Table 2). Four open-label studies described decreases of 30–45% on the Clinician-Administrated PTSD Screen (CAPS) (Kozaric-Kovacic and Pivac, 2007; Mello et al., 2008; Petty et al., 2001; Villarreal et al., 2007), though the other three open-label studies all used different PTSD questionnaires (Pivac et al., 2004; Robert et al., 2005; Stathis et al., 2005) (Table 2). Only one open-label study defined response (decrease CAPS ≥20%) and reported that 64% of patients responded (Villarreal et al., 2007). All RCTpls used different PTSD questionnaires (CAPS, Treatment Outcome PTSD (TOP-8)), Davidson Trauma Scale (DTS, Short PTSD Rating Interview (SPRINT)) with mean decreases of 35–47% compared to 28–52% of patients treated with placebo (Butterfield et al., 2001; Reich et al., 2004; Padala et al., 2006) which reached statistical significance in one RCTpl (Reich et al., 2004). In addition, only one RCTpl reported that 60% of the patients could be classified as responders (CGI-I 1 or 2), but patients treated with placebo showed a similar response rate (Butterfield et al., 2001).

3.6. SAD

Patients with SAD have a persistent fear of one or more social or performance situations in which they are exposed to unfamiliar people or to possible scrutiny by others. The patient fears that he or she will act in a way (or show anxiety symptoms) that will be embarrassing and humiliating, though the patient recognizes that this fear is unreasonable or excessive (DSM-IV, 1994). One open-label study one double-blind crossover study, and two RCTPLs, were conducted with monotherapy of atypical antipsychotics in SAD (Barnett et al., 2002; Schutters et al., 2005; Vaishnavi et al., 2007) (Table 2). The open-label study and one RCTpl used the Liebowitz Social Anxiety Scale (LSAS) to measure efficacy. The open-label study showed a mean decrease of the LSAS of 37%, while the RCTpl reported a mean reduction of the LSAS of 47% compared to 19% in the placebo group, which was not significantly different (Barnett et al., 2002; Schutters et al., 2005). Vaishnavi et al. (2007) used the Brief Social Phobia Scale (BSPS) and showed a decrease of 22% in SAD patients treated with quetiapine compared to 14% of patients treated with placebo, but these results did not reach statistical significance (Vaishnavi et al., 2007). In a double-blind crossover study patients with SAD were randomly exposed to a virtual public speaking task 1 h after placebo or quetiapine. A parallel challenge occurred 1 week later using a counter-balanced

Notes to Table 1

Abbreviations (alphabetical order): ? = unknown, AD = antidepressant, Aug = augmentation, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression Improvement scale, CI = confidence interval, RCTPL = double-blind randomized clinical trial, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Depression Rating Scale, ITT = intention-to-treat, LOCF = Last Observation Carried Forward, Mono = Monotherapy, na = not available, NNT = number needed to treat, OC = obsessive–compulsive, ol = olanzapine, PANNS = Positive and Negative Syndrome Scale, PAS = Psychotic Anxiety Scale, pl = placebo, que = quetiapine, Q300 = quetiapine 300 mg, Q600 = quetiapine 600 mg, RCT = randomized, double-blind trial without placebo arm, RCTpl = randomized, double-blind, placebo-controlled trial, risp = risperidone, RR = relative risk, SDS = Sheehan Disability Scale, TR = Treatment-Refractory, vs = versus, Y-BOCS = Yale–Brown Obsessive–Compulsive Scale.

[a] BPRS Factor I = Brief Psychiatric Rating Scale items: somatic concern, anxiety, guilt feelings, and depression.

[b] Five risperidone patients used antidepressant medication (4 SSRI and 1 TCA) and three placebo patients used antidepressant medication (2 SSRI and 1 TCA).

[c] Olanzapine low (n=65), olanzapine medium (n=64), olanzapine high (n=69), haloperidol (n=69), placebo (n=68).

[d] Short-term phase of 8 weeks (n=16), followed by extension phase of 10 months (n=10).

[e] Quetiapine 300 mg/d (n=175), quetiapine 600 mg/d (n=182), placebo (n=182).

[f] Olanzapine monotherapy (n=168), olanzapine+fluoxetine (n=31), placebo (n=160).

Table 2 Monotherapy of atypical antipsychotics in anxiety disorders (n=22).

Indication Medication	TR or naive	Author	Year of publ.	N	Mean dose [SD] or range (mg/d)	Open-label or RCT	Trial length (weeks)	Decrease on questionnaire (%)	p	Completer/ ITT/LOCF analysis	Completers N (%)	Response criteria; responders N (%)
Generalized anxiety disorder												
Olanzapine	?	Klieser	2000	25	2.5–10	Open	4	CGI ? HAM-A 21.6 (74) STAI X1: 10.6 (19) STAI X2 6.1 (11)	<0.001 ? <0.001 <0.001	?	25 (100)	*No response criteria*
Ziprazidone	TR	Snyderman	2005	13	50.1 [9.6] 20–80	Open	7	HAM-A 11.2 (55) HAM-D 7.1 (56) HAD-A 3,7 (36) SDS 6.8 (35) CGI-S 1.5 (36) CGI-I 2 (54)	<0.001 <0.003 <0.003 =0.014 <0.001	ITT/LOCF	?	Decrease HAM-A ≥ 50%; 7 (54) or CGI-I 1 or 2; 11 (84)
Ziprasidone	TR	Lohoff	2010	62	20–80	RCTpl	8	HAM-A 8.3 (?) zipra, 11.1 (?) pl	ns	ITT/LOCF	57 (92)	*No response criteria*
Quetiapine XR	?	Bandelow	2010	873	Q50 (n=221) or Q150 (n=218) or par (n=217) or pl (n=217)	RCTpl	8	HAM-A: −14.0 (52) Q50-16.0 (60) Q150-14.5 (53) par vs −12.3 (45) pl	<0.05 <.001 <.001	ITT/LOCF	676 (77)	Decrease HAM-A ≥ 50%; 137 (63) 50 que, 153 (71) 150 que, 141 (66) par 20 113 (52) pl
Post-traumatic stress disorder												
Olanzapine	8 naive + 40 TR	Petty	2001	48	14 5–20	Open	8	CAPS 25.4 (30) CGI-I 2.74 HAM-A 7.98 (32) HAM-D 7 (30) BPRS 1.2 (38)	<0.001 <0.001 <0.001 =0.042	Completers	3 (100)	*No response criteria*
Olanzapine (vs n=27 fluphenazine)	TR	Pivac	2004	28	5–10	Open	6	Watson's PTSD scale ? (only graph) PANSS? (only graph) CGI-I 1.57 ol (?) vs 3.15 fl (?)	=0.000 =0.000 <0.05	?	?	*No response criteria*

								PGI-I 1.68 ol (?) vs 3.48 fl (?)	<0.05			
Quetiapine	?	Stathis	2005	6	50–200	Open	6	TSCC 21 (28)	<0.01	ITT	6 (100)	*No response criteria*
Quetiapine	TR	Kozaric-Kovacic	2007	56	335.75 [85.25]	Open	8	CAPS 40.1 (45) CGI-I 4 (71) PANSS 85.8 (63)	<0.001 <0.001 <0.001	Completers	53 (95)	*No response criteria*
Aripiprazole	?	Villarreal	2007	22	12.95	Open	12	CAPS ? PANNS ? HAM-A ? HAM-D ?	=0.011	LOCF	13 (60)	Decrease CAPS ≥ 20%; 14 (64)
Aripiprazole	Naive (n = 7) Use(d) medication (n = 25)	Mello	2008	32	9.6 (4.3, 3.75–15)	Open	16	CAPS 31.3 (38)		ITT/ LOCF	23 (72)	Decrease CAPS ≥ 30%;
Olanzapine	?	Butterfield	2001	15	14.1	RCTpl	10	TOP-8 6.7 (35) ol vs 11.3 (52) pl SPRINT 13.6 (43) ol vs 14,3 (41) pl DTS 34.2 (37) ol vs 39.8 (42) pl SDS 7.7 (39) ol vs 8 (37) pl	ns ns ns ns	LOCF	7/10 (70) ol vs 4/5 (80) pl	CGI-I 1 or 2; 6 (60) ol vs 3 (60) pl
Risperidone[a]	TR	Reich DB	2004	21	2.05	RCTpl	8	CAPS-1 ? CAPS-2 29.6 (47) risp vs 18.6 (28) pl	ns =0.015	ITT/LOCF	9/12 (75) risp vs 7/9 (78) pl	*No response criteria* In text: >50% reduction CAPS-2: p = 0.015
Risperidone	?	Padala	2006	20	2.62	RCTpl	10	TOP-8 ? (only graph) CAPS:? (only graph)	ns ns	?	9/11 (82) risp vs 6/9 (67) pl	*No response criteria*
Post-traumatic stress disorder and insomnia												
Quetiapine	TR	Robert	2005	20	100	Open	6	PSQI 7.9 (50) PSQI-A 2.2 (23)	<0.001 =0.008	ITT/LOCF	18 (90)	*No response criteria*
Social anxiety disorder												
Quetiapine	Naïve (n = 12) TR (n = 1)	Schutters	2005	13	250	Open	12	LSAS ? (37%)	?	LOCF	13 (100)	CGI-I score of 1 or 2; 9 (69%)

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Table 2 (*continued*)

Indication Medication	TR or naive	Author	Year of publ.	N	Mean dose [SD] or range (mg/d)	Open-label or RCT	Trial length (weeks)	Decrease on questionnaire (%)	p	Completer/ ITT/LOCF analysis	Completers N (%)	Response criteria; responders N (%)
Social anxiety disorder												
Quetiapine	?	Vaishnavi	2007	15	147	RCTpl	8	BSPS 10.1 (22) que vs 6 (14) pl	ns	ITT	?	CGI-I 1 or 2; ? (40) que vs ? (0) pl or Reduction BSPS $\geq$ 50% ? (20) que vs ? (0)
Quetiapine	?	Donahue	2009	24	25 and placebo[b]	Double-blind cross-over	2	PRCS 21.9 (?) que vs 22.5 (?) pl	ns	?	20/24 (83)	*No response criteria*
Olanzapine	?	Barnett	2002	12	9	RCTpl	8	BSPS 14 (37) ol vs 3.4 (7) pl SPIN 20,3 (58) ol vs 6 (12) pl LSAS 42.3 (47) ol vs 20.2 (19) pl SDS 6.7 (38) ol vs 2.6 (15) pl	=0.02 =0.01 ns ns	LOCF	4/7 (57) ol vs 3/5 (60, p=?) pl	CGI-I 1 or 2; 3/5 (60) ol vs 0 pl
Panic disorder												
Risperidone vs paroxetine	?	Prosser	2009	56	0.53 (0.125–1) risp vs 30 (n=22) par +40 (n=1) par	RCT	8	CGI 1.6 (36) risp vs 1.2 (32) par PDSS 5.6 (42) risp vs 4 (33) par HAM-A 11.3 (45) risp vs 11.5 (42) par SPAS-P +2.2 (3) risp vs 2.9 (3) par	ns ns ns ns	ITT/LOCF	20/32 (61) risp vs 9/23 (39) par	*No response criteria*

Anxiety for dental surgery												
Ziprasidone	naive	Wilner	2002	90 (3×30)	Single oral dose of ziprasidone 20 mg vs diazepam 10 mg vs pl	RCTpl	–	VAS scale for anxiety 0–10: graph only (±6.5 to 3 zi) zipra vs pl zipra vs diazepam	p=0.05 ns	?	90 (100)	?
Obsessive–compulsive disorder												
Clozapine	TR	McDougle	1995	12	?	Open	10	Y-BOCS ns, CGI ns, HDRS ns			12 (100)	Response criteria: ? No responders
Arpiprazole	5 naïve 3 TR	Connor	2005	8	10–30	Open	8	Y-BOCS 6.3 (26) CGI-I 3	ns	completers	5 (71)	Decrease Y-BOCS ≥ 30% and CGI-I 1 or 2; 2/5 (40)

Abbreviations (alphabetical order): ? = unknown, Aug = augmentation, BPRS = Brief Psychiatric Rating Scale, BSPS = Brief Social Phobia Scale, CAPS = Clinician-Administered PTSD Screen, CAPS-1 = Clinician-Administered PTSD Screen 1-month version, CAPS-2: Clinician-Administered PTSD Screen 1-week version, CGI = Clinical Global Impression score, CGI-I = Clinical Global Impression Improvement scale, CGI-S = Clinical Global Impression Severity of Symptoms scale, RCTPL = double-blind randomized clinical trial, DTS = Davidson Trauma Scale, esc = escitalopram, fl = fluphenazin, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Depression Rating Scale, ITT = intention-to-treat, LOCF = Last Observation Carried Forward, LSAS = Liebowitz Social Anxiety Scale, Mono = Monotherapy, OC = obsessive–compulsive, ol = olanzapine, PANNS = Positive and Negative Syndrome Scale, par = paroxetine, PGI-I = Patient Global Impression Improvement Scale, pl = placebo, PRCS = Personal Report of Confidence as a Speaker PSQI = Pittsburgh Sleep Quality Index, PSQI-A = Pittsburgh Sleep Quality Index Addendum, que = quetiapine, Q50 = quetiapine 50 mg, Q150 = quetiapine 150 mg, Q300 = quetiapine 300 mg, Q600 = quetiapine 600 mg, RCT = randomized clinical trial, risp = risperidone, RR = relative risk, SDS = Sheehan Disability Scale, SNRI = Serotonin Noradrenergic Reuptake Inhibitor, SPIN = Social Phobia Inventory, RCT = randomized, double-blind trial without placebo arm, RCTpl = randomized, double-blind, placebo-controlled trial, SPAS-P = The Sheehan Panic Anxiety Scale-Patient, SPRINT = Short PTSD Rating Interview, STAI = State-Trait, Anxiety Inventory, TOP-8 = Treatment Outcome PTSD scale, TSCC = Traumatic Symptom Checklist in Children, TR = Treatment-Refractory, VAS = Visual analogue scale, vs = versus, Y-BOCS = Yale–Brown Obsessive-Scale, zipra = ziprazidone.

[a]Five risperidone patients used antidepressant medication (4 Serotonin Reuptake Inhibitor (SSRI), 1 Tricyclic Antidepressant (TCA)) and 3 placebo patients used antidepressant medication (2 SSRI and 1 TCA).

[b]Two virtual public speaking exposures: 1 preceded by quetiapine 25 mg and the other preceded by placebo.

Table 3 Augmentation of atypical antipsychotics in anxiety disorders (n = 48).

Indication Medication	TR or naïve + n	Author Year of publ.	Mean dose [SD] or range (mg/d)	Open-label or RCT Trial length (weeks)	Decrease on questionnaire (%)	p	Completer/ ITT/LOCF analysis	Completers N (%)	Response criteria; responders N (%)
Panic disorder									
Olanzapine PD: n = 15 PD + AG: n = 16	TR 31	Sepede et al., 2006	5	Open 12	N panic attacks:4.5 (82) PD and 4.5 (71) PDAG ACQ: 14.5 (79) PD and 29.9 (70) PDAG HAM-A: 14.2 (73) PD and 20.8 (76) PDAG HAM-D: 6.8 (70) PD and 6.8 (49) PDAG	<0.001 <0.001 <0.001 <0.001	?	26 (84) PD (n = 13) vs PD + AG (n = 13)	CGI-I 1 or 2 and reduction panic attacks ≥ 50%; 21 (82)
Olanzapine	TR 15	Hollifield et al., 2005	12.3 (2.5–20)	Open 8	PAI: number attacks/wk 6.1 to 1.1 anticipatory anxiety: 32% to 8% of the day PPPD: ? CGI-S: 4.6 to 2.6	<0.01 =0.01 <0.01 <0.000	?	10 (67)	*No response criteria*
Aripiprazole	TR 10	Hoge et al., 2008	10.5 (4.95; 5–30)	Open 8	PDSS 2.2 (14) CGI-S 0.8 (17)	ns <0.05	ITT/LOCF	7 (70)	CGI-I 1 or 2; 1 (10)
Generalized anxiety disorder									
Quetiapine	TR 22	Simon et al., 2008	120.5 (25–400)	RCTpl 8	HAM-A 2.6 (16) que vs 0.3 (2) pl CGI-S 0.7 (20) que vs 0.6 (14) pl MADRS 1.2 (10) que vs 0.72 (58) pl	ns ns ns	ITT	6/11 (55) que vs 10/11 (91) pl	CGI-I 1 or 2; 6 (54) que vs 5 (45) pl
Aripiprazole	TR 9	Menza et al., 2007	13.9	Open 6	HAM-A 12 (46) CGI-I: 8 out of 9 had a CGI-I of 1 or 2	<0.0001	?	8 (89)	Decrease HAM-A ≥ 50% 5 (56)
Risperidone PD (n = 7) SAD (n = 7) GAD (n = 16)	TR 30	Simon et al., 2006	1.12 [0.68] (0.25–3)	Open 8	HAM-A 5.97 (26) CGI-S 1.53 (31) HAM-D 3.84 (25) Q-LES-Q + 5.33 (10) SDS 5.83 (40) ASI 6.5 (23) PD pts: PDSS (30) PD pts: panic	=0.0005 <0.000 =0.0006 =0.017 =0.0001 =0.035 =0.046 ns	?	21 (70)	*No response criteria*

					CGI-S 1 (21) SAD pts: LSAS 42.9 (53) GAD pts: HAM-A 6.75 (27)	=0.015, =0.0 06			
Risperidone	TR 39	Brawman-Mintzer et al., 2005	1.1 [0.4] (0.5–1.5)	RCTpl 5	HAM-A 9.8 (44) risp vs 6.2 (30) pl HAM-A psychic anxiety 6.3 (?) risp vs 3.8 (?) pl	=0.034 =0.047	ITT	15/19 (79) risp vs 16/20 (80) pl	CGI-I 1 or 2; 11 (58) risp vs 7 (35) pl
Risperidone	TR 417	Pandina 2007	?	RCTpl 4	PaRTS-A 8.5 (?) risp vs 7.6 (?) pl	ns	?	?	?
Aripiprazole	TR 17[a]	Worthington et al., 2005	7.5–30	Open 12	CGI-S 1.6 (30) CGI-I 2.4	<0.001 ?	ITT/ LOCF	12 (71)	CGI-I 1 or 2; 10 (59)
Aripiprazole	TR 13	Hoge et al., 2008	10.5 (4.95; 5–30)	Open 8	PDSS 6.7 (29) CGI-S 1.2 (25)	≤0.01 ≤0.01	ITT/LOCF	10/13 (77)	CGI-I 1 or 2; 3 (23)
Olanzapine	TR 24	Pollack et al., 2006	8.7 [7.1] (2.5–20)	RCTpl 6	HAM-A 7 (40) ol vs 3.9 (17) pl HAM-D 5.1 (40) ol vs 2.2 (14) pl ASI 7.6 (31) ol vs +0.4 (2) pl	ns ns ns	?	7/12 (58) ol vs 10/12 (82) pl	Decrease HAM-A≥50%; 5 (55) ol vs 1 (8, p=0.046) pl or a CGI-S <3; 6 (67) ol vs 1 (8, p=0.02) pl
Post-traumatic stress disorder									
Quetiapine Aug (n=18) Mono (n=2)	TR 20	Hamner et al., 2003	100	Open 6	CAPS 22.3 (25) CGI-I: 11 had 2 or 3, 5 had 1 and 4 had 0 PANSS 8.7 (11)	<0.0005 <0.007	LOCF	19 (95)	Decrease CAPS-2≥20%; 12 (63) CGI-I 1 or 2; 11 (58)
Quetiapine	TR 68	Sokolski et al., 2003	155 [130]	Open 180 days	No questionnaire		Completer	?	*No response criteria*
Quetiapine	TR 15	Ahearn et al., 2006	216	Open 8	CAPS 34 (42) TOP-8 9 (45) DTS 35 (44) CGI-S 1 (?) PSQI 12.5 (42) HAM-D 10.5 (58)	=0.001 =0.002 =0.0033 =0.0045 =0.004 =0.0029	LOCF	14 (93)	Decrease CAPS≥30% and CGI-I≤2; 8 (53)
Quetiapine	? (n=175) vs prazosin (n=62)	Byers 2010	101 (6 months) que, 135 (6 years) que (25–600)	Historical prospective cohort 6 months +3–6 years	Short-term effectiveness 62% improvement, no questionnaire	–	–	? (76) long term	

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Table 3 (*continued*)

Indication Medication	TR or naïve+n	Author Year of publ.	Mean dose [SD] or range (mg/d)	Open-label or RCT Trial length (weeks)	Decrease on questionnaire (%)	p	Completer/ ITT/LOCF analysis	Completers N (%)	Response criteria; responders N (%)
Post-traumatic stress disorder									
Risperidone	TR 17	David 2004	2.3 [0.6] (1–3)	Open 12	CAPS 12 (14) PANNS 12 (13) CGI-I 1.2 (21) HAM-D 0.7 (4) HAM-A 1.5 (6)	=0.002 =0.002 =0.001 ns ns	LOCF	13 (76)	*No response criteria* CGI-I=2; 8/17 (47)
Risperidone	TR 37	Hamner et al., 2003	2.5 [1.25] (1–6)	RCTpl 5	CAPS 9 (10) risp vs 10.1 (11) pl CAPS-intrusion 4.6 (?) risp vs 2.2 (?) pl PANNS 10 (12) risp vs 2.3 (3) pl	ns ns <0.05	LOCF	10/19 (53) risp vs 12/18 (67) pl	*No response criteria*
Risperidone	? 16	Monnelly et al., 2003	0.57 [0.13] (0.5–2.0)	RCTpl 6	OAS-M irritability 2 (29) risp vs 1 (17) pl OAS-total PCL-M cluster B 4 (17) risp vs 0 pl Other PCL clusters	=0.04 ns =0.001 ns	?	7/8 (88) risp vs 8/8 (100) pl	*No response criteria*
Risperidone	? 65	Bartzokis et al., 2005	3	RCTpl 16	CAPS 14.3 (14) risp vs 4.6 (0.5) pl Re-experiencing subscale (CAPS-B) 5 (18) risp vs 1.8 (7) pl Avoidance scale (CAPS-C) 3.7 (9) risp vs 1.7 (4) pl Hyperarous al subscale (CAPS-D) 5.5 (17) risp vs 1.1 (4) pl HAM-A 7.4 (32) risp vs 2 (8) pl HAM-D 3.7 (18) risp vs 1.4 (6) pl PANNS 3.5 (21) risp vs 0.13 (1) pl	<0.05 ns ns <0.01 <0.001 ns <0.01	Completers	22/33 (67) risp vs 26/32 (81) pl	Decrease CAPS≥20; 9 (27) risp vs 1 (3) pl (p=0.002)
Risperidone	? 45	Rothbaum 2008	2.1	RCTpl 8	CAPS 23.1 (30) risp vs 23.5 (31) pl CGI-I 2 risp vs 2.3 pl	ns ns	Completers +LOCF DTS +BDI	20 (44)	*No response criteria*
Olanzapine	TR 19	Stein et al., 2002	(10–20)	RCTpl 8	CAPS 14.8 (17) ol vs 2.7 (3) pl	<0.05,	LOCF PSQI: completers	7/10 (70) ol vs 7/9 (78) pl	CGI-I 1 or 2; 3 (30) ol vs

					CES-D 5.3 (14) ol vs 4.9 (14) pl	<0.03			1 (11) pl (ns)
					PSQI 3.3 (20) ol vs 1.6 (10) pl	=0.01			
Ziprasidone	TR 24	Kellner et al., 2010	80–160	RCTpl	PDS, BDI na	na	na	b	na
Obsessive–compulsive disorder									
Olanzapine	TR 10	Weiss et al., 1995	?	Open 8	?	?	?	9 (90)	*No response criteria*
Olanzapine	TR 23	Bogetto et al., 2000	5	Open 12	Y-BOCS 8.0 (30)	?	?	23 (100)	Decrease Y-BOCS ≥ 35% and CGI-I ≤ 2; 10 (44)
Olanzapine	TR 10	Koran et al., 2000	(2.5–10)	Open 8	Y-BOCS 4.6 (16)	?	?	9 (90)	Decrease Y-BOCS ≥ 25%; 3 (33) and CGI-I ≤ 2; 1 (11)
Olanzapine	? 9	Francobandiera, 2002	?	Open 6	Y-BOCS ? CGI ?	?	?	8 (89)	? 6/10 (60)
Olanzapine	TR 21	D'Amico et al., 2003	10	Open 12	Y-BOCS 7.0 (26)	?	?	18 (86)	Decrease Y-BOCS ≥ 35% and CGI-I ≤ 2; 7 (39)
Olanzapine	TR 50	Maina et al., 2008	ol 5.3 [2.6] (2.5–10), risp 2.1 [0.6] (1–3)	RCT 8	Y-BOCS 7.5 (25) risp vs 8.4 (27) ol	ns	?	22/25 (88) risp vs 21/25 (84) ol	Decrease Y-BOCS ≥ 35% and CGI-I ≤ 2; 11 (44) risp vs 12 (48) ol
Olanzapine	TR 26	Bystritsky et al., 2004	11.2 ± 6.5(5–20)	RCTpl 6	Y-BOCS 4.2 (?) ol vs +0.5 (?) pl	=0.04	ITT	11 (85) ol vs 13 (100) pl	Decrease Y-BOCS ≥ 25%; 6 (46) ol vs 0 pl
Quetiapine	TR 8	Mohr et al., 2002	128.6	Open 6	Y-BOCS 5.8 (23)	?	Completer	8 (100)	CGI-I ≤ 2; 4 (50)
Quetiapine	TR 10	Denys et al., 2002	200	Open 8	Y-BOCS 10.6 (34)	=0.002	ITT	10 (100)	Decrease Y-BOCS ≥ 50%; 3 (30)
Quetiapine	TR 14	Atmaca et al., 2002	50–200	Open 8	Y-BOCS 10.7 (44)	?	ITT	14 (100)	Decrease Y-BOCS ≥ 60; 9 (64), and decrease Y-BOCS ≥ 30%; 10 (71)

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Table 3 (*continued*)

Indication Medication	TR or naïve + n	Author Year of publ.	Mean dose [SD] or range (mg/d)	Open-label or RCT Trial length (weeks)	Decrease on questionnaire (%)	p	Completer/ ITT/LOCF analysis	Completers N (%)	Response criteria; responders N (%)
Quetiapine	TR	Sevincok and	150	Open	Y-BOCS 7(19)	?	ITT	8 (100)	Decrease
Obsessive—compulsive disorder									
	8	Topuz, 2003		10					Y-BOCS ≥ 25%; 2 (25)
Quetiapine	TR 17	Misri and Milis, 2004	25—300	Open 12	Y-BOCS 14.5 (60)	<0.001	completer	14 (82)	Decrease Y-BOCS + CGI-S ≥ 50%; 11(79)
Quetiapine	TR 30	Bogan et al., 2005	25—200 S1: 169, S2: 116 [c]	Open 8	Y-BOCS S1: 4.4 (16) and S2: 1.6 (6)	=0.01 ns	ITT	25 (83)	Decrease Y-BOCS ≥ 25%: S1: 5/16 (31), S2: 2/14 (14)
Quetiapine	TR 40	Denys et al., 2004	200—300	RCTpl 8	Y-BOCS 9 (32) que vs 2 (9) pl	<0.001	ITT	40 (100)	Decrease Y-BOCS ≥ 35% and CGI-I ≤ 2; 8/20 (40) que vs 2/20 (10) pl
Quetiapine	TR 21	Fineberg et al., 2005	215	RCTpl 16	Y-BOCS 3.4 (14) que vs 1.4 (6) pl	ns	?	10/ 11 (91) que vs 9/10 (90) pl	Decrease Y-BOCS ≥ 25%; 3 (27) que vs 0 pl
Quetiapine	TR 41	Carey et al., 2005	169	RCTpl 6	Y-BOCS 7.1 (?) que vs 7.2 (?) pl	?	?	39 (95) (2 withdrawn, group unknown)	Decrease Y-BOCS ≥ 25% and CGI-I ≤ 2: 8/20 (40) que vs 10/21 (48) pl
Quetiapine	TR 40	Kordon et al., 2008	400—600	RCTpl 12	Y-BOCS 5.2 (22) que vs 3.9 (15) pl	ns	ITT/LOCF	12/18 (67) que vs 17/20 (85) pl (ns)	Decrease Y-BOCS ≥ 35%)\: ? CGI-I = 2; 4/18 (22) que vs 6/20 (30) pl
Quetiapine	Naive 76	Vulink	300—450	RCTpl 10	Y-BOCS 11.9 (43) que vs 7.8 (30) pl CGI-S 1.4 (26) que vs 1.3 (24) pl CGI-I 2.1 (51) que vs 1.4 (35) pl HAM-A 6.6 (50) que vs 3.8 (28) pl	=0.009 ns =0.023 =0.05	ITT/LOCF	31/39 (79) que vs 35/37 (95) pl	Decrease Y-BOCS ≥ 25% and CGI-I ≤ 2: 22/39 (56) que vs 15/37 (41) pl
Quetiapine or clomipramine	TR 31	Diniz et al., 2010	50—200	RCT	Y-BOCS 4 (18) que vs 0.4 (2) clomi	ns	ITT/LOCF	9/16 (56) que vs 9/15 (60) clomi	Decrease Y-BOCS ≥ 35%

					CGI-I 2: 8/16 que vs 4/15 clomi				and CGI-I ≤ 2: 4/16 (25) que vs 1/15 (7) clomi
Risperidone	TR 14	Ravizza et al., 1996	?	Open ?	?	?	?	?	Response: 7(50) no criteria
Risperidone	TR 20	Pfanner et al., 2000	3.0	Open 8	?	?	?	20 (100)	Response: all patients, no criteria
Risperidone	TR 21	Saxena et al., 1996	2.75	Open	?	?	?	16 (76)	?
Risperidone	TR 36 [c]	McDougle et al., 2000	2.2 (0.7)	RCTpl 6	Y-BOCS 8.7 (32) risp vs 2.6 (9) pl HAM-A 4.1 (31) risp vs 1.9 (14) pl HAM-D ? CGI-I ?	=0.005 =0.003 <0.001	Completers (3 dropouts in first week not included)	18/20 (90) risp vs 15/16 (94) pl	Decrease Y-BOCS ≥ 35%, final Y-BOCS ≤ 16 and CGI-I 1 or 2; 9/18 (50) risp vs 0/15 (0) pl ($p < 0.005$)
Risperidone	TR [d] 45	Erzegovesi et al., 2005	0.5	RCTpl 6	Y-BOCS: Responders: 0.6 (4) risp vs 4.2 (28) pl Nonresponders:7.9 (26) risp vs 1.8 (7) pl	ns =0.001	?	39 (87)	Decrease Y-BOCS ≥ 35% + CGI-I 1 or 2; Nonresponders5/10 (50) risp vs 2/10 (20) pl
Risperidone (n = 7), quetiapine (n = 19), olanzapine (n = 18)	TR 44	Matsunaga et al., 2009	3.1 (1.9, 1–5) risp, 60.0 (37.3, 25–100) que, 5.1 (3.2, 1–10) olan	RCT 1 year	Y-BOCS 10 (40) risp, que and ol	?	ITT/ LOCF	44 (100)	Decrease Y-BOCS ≥ 50%; ? (32) risp, que and ol
Aripiprazole	TR 9	Pessina et al., 2009	11.2 (5.2; 5–20)	Open	Y-BOCS 4.8 (20) CGI-S 0.8 (16)	<0.01 <0.01	completers	8/9 (89)	Decrease Y-BOCS ≥ 25%: 3/9 (33)

=? = unknown, ACQ = Agoraphobic Cognitions Questionnaire, AG = agoraphobia, ASI = Anxiety Sensitivity Index, Aug = Augmentation, BDI = Beck Depression Inventory, CES-D = self-rated Center for Epidemiologic Studies Depression Scale, CAPS = Clinician-Administered PTSD Screen, CGI-I = Clinical Global Impression Improvement score, CGI-S = Clinical Global Improvement-Severity scale, DTS = Davidson Trauma Scale, fluo = fluoxetine, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Depression Rating Scale, ITT = intention-to-treat, LSAS = Liebowitz Social Anxiety Scale, MADRS = Montgomery Asberg Depression Rating Scale, Mono = Monotherapy, na = not available, OAS-M = Overt Aggression Scale, ol = olanzapine, PAI = Panic Attack Inventory, PANNS = Positive and Negative Syndrome Scale, PaRTS-A = Patient-Rated Troubling Symptoms for Anxiety, PCL-M = PTSD checklist, Military Version, PDS = Post-traumatic Diagnostic Scale, PDSS = Panic Disorder Severity Scale, pl = placebo, PPPD = Physicians Panic and Phobic Disorders Scale, PSQI = Pittsburgh Sleep Quality Index, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, q = quetiapine RCT = randomized, double-blind trial without placebo arm, RCTpl = randomized, double-blind, placebo-controlled trial, risp = risperidone, SDS = Sheehan Disability Scale, Top- = Treatment Outcome PTSD Scale, Modified for outpatients, TR = Treatment-Refractory vs = versus, Y-BOCS = Yale–Brown Obsessive–Compulsive Scale.

[a] = PD (n = 2), SAD (n = 2), GAD (n = 4), PTSD (n = 2), OCD (n = 1), MDD (n = 6).

[b] = stopped trial: 3 of first 7 patients dropped out because of severe side effects: deblinding: all 3 used ziprasidone compared to placebo in 4 patients who stayed in the trial.

[c] = risperidone (n = 20), placebo (n = 16).

[d] responders (n = 19) and nonresponders (n = 20) to 12 weeks fluvoxamine 150–300 mg/d.

cross-over (within subject) design for the medication-placebo order between the two sessions. Quetiapine was not effective in alleviating SAD symptoms in individuals with fears of public speaking (Donahue et al., 2009). Except for the double-blind crossover study, the other three studies defined response rate as a CGI-I score of 1 or 2, with 69% responders in the open-label trial and 40–60% responders in both RCTpls, compared to none of the patients treated with placebo. However, a statistical significant difference in responders was only found in one RCTpl (Barnett et al., 2002).

3.7. Anxiety for dental surgery

Wilner et al. (2002) included 90 nonpsychotic subjects who were anxious before undergoing minor dental surgery and compared the anxiolytic efficacy of ziprasidone (single dose of 20 mg, n = 30) with that of 10 mg diazepam (n = 30) and placebo (n = 30) in a randomized, parallel-group, double-blind study (Table 2). At 3 h postdose, the anxiolytic effect of ziprasidone was significantly greater than that of placebo and somewhat greater than that of diazepam. Diazepam showed a significantly greater anxiolytic effect than placebo at 1 h, but not at 3 h (Wilner et al., 2002).

3.8. PD

Panic disorder is a condition in which the person with the disorder suffers recurrent, unexpected panic attacks. Panic attacks are characterized by a sudden onset of intense anxiety or fear, and accompanied by palpitations, shortness of breath, sweating, and trembling.

Patients with PD plus agoraphobia experience sudden, unexpected panic attacks that cause them to fear being in a place where help might not be available; or, they may experience sudden panic attacks in specific, known situations, and fear those situations or places that may trigger attacks (DSM-IV, 1994).

In one randomized controlled trial of risperidone versus paroxetine, HAM-A scores decreased 45% and 42% respectively, without significant differences between both medications (Prosser et al., 2009).

3.9. OCD

Obsessive–compulsive disorder (OCD) is a chronic and disabling disease characterized by intrusive, unwanted and recurrent thoughts (obsessions) and/or repetitive ritualistic behaviours (DSM-IV, 1994). One small open-label study reported a small improvement of OCD symptoms in patients treated with aripiprazole who showed a mean decrease of 26% on the Y-BOCS (ns) (Connor et al., 2005).,while another open-label study with clozapine did not reveal any improvement of OCD symptoms (Table 2) (McDougle et al., 1995). No RCTs have been conducted so far.

Taken together, open-label studies of monotherapy of atypical antipsychotics showed a mean decrease of anxiety questionnaires between 26 and 74% with 40–84% responders, one RCT showed a mean decrease between 36 and 45%; while four out of eight RCTpls showed a significantly higher decrease on anxiety questionnaires (47–60%) in patients with GAD, SAD, PTSS and anxiety for dental surgery when they were treated with monotherapy of atypical antipsychotics compared to placebo (12–45%).The number of responders was 60–71% in patients treated with atypical antipsychotics compared to 0–52% of patients treated with placebo. However, four RCTpls of monotherapy with atypical antipsychotics showed negative results in patients with GAD, PTSS, and SAD.

The proportion of patients with anxiety disorders or OCD completing open-label studies with monotherapy of atypical antipsychotics varied between 60 and 100%, while 57–82% of patients treated with atypical antipsychotics in RCTs completed the trial compared to 60–80% of the patients treated with placebo ($Z = 0.0$, $p > 0.05$).

3.10. PD

Three open-label studies reported about the successful addition of olanzapine to SSRIs in patients with PD (Table 3) (Hoge et al., 2008; Hollifield et al., 2005; Sepede et al., 2006). The mean number of panic attacks decreased with 82% in PD patients in two studies, but another study did not show significant differences in severity of panic symptoms. One of the open-label studies showing a reduction in panic attacks also reported a response rate (CGI-I 1 or 2 and reduction of panic attacks $\geq 50\%$) in 82% of patients (Sepede et al., 2006), while the negative open-label study only showed response (CGI-I ≤ 2) in 1 (10%) patient.

3.11. PTSD

Four open-label trials, a historical prospective cohort study and six RCTpls of addition of atypical antipsychotics have been conducted in patients with PTSD (Table 3). Two open-label studies with quetiapine, and one with risperidone reported mean decreases on the Clinician-Administered PTSD Scale (CAPS) of 14–42% (Ahearn et al., 2006; Hamner et al., 2003; Sokolski et al., 2003), while one open-label study and the historical cohort study did not use an anxiety questionnaire (Sokolski et al., 2003). Two open-label studies defined response criteria (decrease CAPS $\geq 20\%$ or CGI-I 1 or 2; decrease CAPS $\geq 30\%$ and CGI-I 1 or 2) and reported response rates of 53–63% (Ahearn et al., 2006; Hamner et al., 2003). One RCTpl with risperidone and one RCTpl with olanzapine showed mean decreases of the CAPS of 14–17%, while patients treated with placebo showed mean decreases of 0.5–3% on the CAPS (Bartzokis et al., 2005; Stein et al., 2002). Two other RCTpls did not show significant differences in changes in CAPS scores between patients treated with risperidone compared to placebo. One RCT used different questionnaires and reported decreases on the Overt Agression Scale (OAS) of 29% in patients treated with risperidone and 17% in patients on placebo (ns), while the PTSD Checklist-Military version (PCL-M) Cluster B decreased 17% compared to no change in placebo-treated patients ($p = 0.001$) (Monnelly et al., 2003). One RCTpl with ziprasidone was stopped after the inclusion of 7 patients because three of the first seven patients terminated study participation because of intolerable side effects (Kellner et al., 2010). Response rates in two RCTpls (decrease CAPS $\geq 20\%$ and CGI-I 1 or 2) varied between 27 and 30% in patients treated with addition of atypical antipsychotics, compared to 3–11% of

patients treated with placebo (Bartzokis et al., 2005; Stein et al., 2002). A significant difference in response rates between atypical antipsychotics and placebo was only found in one RCTpl (Bartzokis et al., 2005).

3.12. GAD

Five open-label studies and three RCTpls described efficacy of addition of atypical antipsychotics to SSRIs in patients with GAD (Table 3). Three open-label trials described mean reductions of the HAM-A of 26–69% (Katzman et al., 2008; Menza et al., 2007; Simon et al., 2006), while two open-label study showed a mean decrease on the CGI-S of 25–30% (Hoge et al., 2008; Worthington, III et al., 2005). Response rates (decrease HAM-A ≥ 50%; CGI-I 1 or 2) were reported in three open-label trials and varied between 23 and 59% of patients (Menza et al., 2007; Worthington, III et al., 2005). Mean HAM-A scores decreased 16–44% in patients treated with addition of atypical antipsychotics in three RCTpls, while a mean reduction of 2–30% was reported in patients treated with placebo (Brawman-Mintzer et al., 2005; Pollack et al., 2006; Simon et al., 2008). One in three RCTpls showed a significant difference in HAM-A scores between patients treated with atypical antipsychotics compared to controls (Brawman-Mintzer et al., 2005). All three RCTpls defined response rates (CGI-I 1 or 2; decrease HAM-A ≥ 50% or CGI-S < 3) and reported that 54–67% of patients treated with augmentation of atypical antipsychotics could be classified as responder, while 8–45% of patients treated with placebo responded (Brawman-Mintzer et al., 2005; Pollack et al., 2006; Simon et al., 2008). Interestingly, one RCTpl with augmentation of olanzapine in patients with GAD showed a significant higher proportion of patients responding to olanzapine compared to placebo (response was defined as a decrease HAM-A ≥ 50% or CGI-S < 3), whereas no significant difference was found in decrease of HAM-A scores between patients treated with olanzapine or placebo (Pollack et al., 2006). Another RCTpl with risperidone showed opposite results with a significant difference in decrease of HAM-A scores in patients with GAD, but no significant difference was found in number of responders (CGI-I 1 or 2) (Brawman-Mintzer et al., 2005).

3.13. OCD

Fifteen open-label studies, three RCTs, and eight RCTpls of augmentation of atypical antipsychotics showed promising results in patients with OCD (Table 3). Mean Y-BOCS scores decreased between 6 and 60% in the open-label studies (Atmaca et al., 2002; Bogan et al., 2005; Bogetto et al., 2000; D'Amico et al., 2003; Denys et al., 2002; Francobandiera, 2002; Koran et al., 2000; Misri and Milis, 2004; Mohr et al., 2002; Pessina et al., 2009; Pfanner et al., 2000; Ravizza et al., 1996; Sevincok and Topuz, 2003; Weiss et al., 1995). Three RCTs compared olanzapine, quetiapine, risperidone and clomipramine addition and reported mean decreases of the Y-BOCS of 18–40% in patients treated with add-on of atypical antipsychotics and 2% in patients who received add-on therapy with clomipramine (Maina et al., 2008; Diniz et al., 2010; Matsunaga et al., 2009). Response rate (defined as decrease on the Y-BOCS ≥ 25–60% and/ or CGI ≤ 2 or decrease on the Y-BOCS + CGI-S ≥ 50%) varied between 33 and 79% in the open-label studies, and 25–48% in the RCTs. Eight RCTpls showed mean Y-BOCS decreases of 14–43% in patients augmented with atypical antipsychotics, compared to 6–30% of patients receiving placebo addition (Bystritsky et al., 2004; Carey et al., 2005; Denys et al., 2004; Erzegovesi et al., 2005; Fineberg et al., 2005; Kordon et al., 2008; McDougle et al., 2000; Saxena et al., 1996; Vulink et al., 2009). RCTpls reported response rates (decrease on the Y-BOCS ≥ 25 or 35% and CGI ≤ 2 in four RCTs) of 22–56% of patients augmented with atypical antipsychotics compared to 0–48% in patients receiving placebo addition. Five RCTpls showed significantly higher number of responders in patients receiving augmentation with atypical antipsychotics compared to controls (Bystritsky et al., 2004; Denys et al., 2004; Erzegovesi et al., 2005; McDougle et al., 2000; Vulink et al., 2009), compared to three RCTpls without beneficial results (Carey et al., 2005; Fineberg et al., 2005; Kordon et al., 2008) and one RCTpl did not mention a comparison between patients treated with atypical antipsychotics and patients treated with placebo (Saxena et al., 1996).

Taken together, open-label studies of augmentation of atypical antipsychotics showed a mean decrease of anxiety questionnaires between 6 and 79% with 10–82% responders, three RCTs showed a mean decrease between 18 and 40% (with 25–48% responders); while nine out of 17 RCTpls showed a significantly higher decrease on anxiety questionnaires (14–50%) in patients with GAD, SAD, PTSS and anxiety for dental surgery when they were treated with augmentation of atypical antipsychotics compared to placebo (0.5–30%). The number of responders was 27–58% in patients treated with atypical antipsychotics compared to 0–41% of patients treated with placebo. However, eight RCTpls showed negative results and one RCTpl was not completed because severe side effects in three of the first seven patients.

The proportion of patients with anxiety disorders or OCD completing open-label treatment studies of augmentation of atypical antipsychotics varied between 67 and 100%. The proportion of patients treated with augmentation of atypical antipsychotics who completed a RCTpl (53–100%) was significantly lower compared to patients using placebo (67–100%; $Z = -2$, 0, $p = 0.041$). Adverse events were a common cause of withdrawal.

4. Discussion

This is the first narrative review reporting on the use of atypical antipsychotics in monotherapy or augmentation in patients with primary anxiety disorders or anxiety (disorders) comorbid to schizophrenia, BPD and MDD. We included 49 open-label trials, 32 randomized, placebo-controlled trials, four randomized controlled trials without placebo arm and one double-blind crossover study with almost 6000 patients (open-label: 1710, randomized: 4145). Firstly, atypical antipsychotics decreased mean scores of anxiety questionnaires (24–80%) in open-label studies in patients with secondary anxiety disorders comorbid to schizophrenia, BPD and MDD, while in RCTpls a mean decrease of 53–70% was reported in patients treated with atypical antipsychotics compared to 26–48% in patients treated with placebo. Three out of four RCTpls that used an anxiety questionnaire in patients with BPD, MDD and secondary anxiety disorders showed significant decreases of anxiety symptoms compared to patients treated with placebo. However, two out of ten open-label studies and two out of six RCTpls did not use an anxiety questionnaire. In addition, response was defined only in two RCTpls in patients with BPD or

MDD and secondary anxiety disorders and one open-label study of patients with schizophrenia and OCD. Secondly, in patients with primary anxiety disorders, open-label studies of monotherapy of atypical antipsychotics showed a mean decrease of anxiety questionnaires between 26 and 74%, while 40–84% of the patients could be classified as responders. Similar results were found in four out of eight RCTpls showing a significantly higher decrease on anxiety questionnaires (47–60%) compared to placebo (12–45%) and a higher number of responders (60–71%) compared to placebo (0–52%). All included trials used an anxiety questionnaire. However, the majority of the included trials (seven open-label trials, four RCTpls, and one double-blind crossover trial) did not define response criteria. Thirdly, open-label studies of augmentation of atypical antipsychotics in patients with primary anxiety disorders showed a mean decrease of anxiety questionnaires between 6 and 79%, similar with nine out of 17 RCTpls showing a significantly higher decrease on anxiety questionnaires (14–50%) compared to placebo (0.5–30%) and a higher number of responders (27–58%) compared to placebo (0–41%). However, seven open-label studies did not use an anxiety questionnaire, while 12 open-label studies and two RCTpls did not define response criteria.

Only one RCT in patients with bipolar disorder and comorbid anxiety compared monotherapy of atypical antipsychotics to augmentation therapy and treatment with placebo. The likelihood of achieving HAM-A response was significantly higher in augmentation treatment compared to monotherapy of atypical antipsychotics or placebo treatment (Tohen et al., 2007). Therefore, larger, double-blind placebo-controlled trials are needed that compare SSRIs to monotherapy or augmentation therapy of atypical antipsychotics and placebo in patients with primary and secondary anxiety disorders. Two other limitations in studies including patients with anxiety comorbid to schizophrenia, BPD and MDD, are the absence of a detailed description of various DSM-IV anxiety disorders in the majority of trials and only changes in HAM-A scores or items with respect to anxiety of general psychopathology checklists were reported. Publication bias is another limitation that may have influenced our results. We reported in our results section that we used a trial result register to minimize publication bias, though we were not able to include results of three completed trials of atypical antipsychotics in primary anxiety disorders.

Although atypical antipsychotics show promising results in the treatment of anxiety disorders, several side effects, especially somnolence, sedation, weight gain, and hyperlipidemia, may limit their use. Besides impairing health, these side effects may be a source of non-compliance and of premature discontinuation of treatment. Higher dropout rates were indeed found in the majority of RCTpls in patients treated with atypical antipsychotics compared to placebo. However, except for one patient with increased cardiac enzymes (Kordon et al., 2008), no serious side effects were reported in the studies reviewed here.

In conclusion, an increasing number of RCTpls show promising results in 27–71% of patients with primary or comorbid anxiety disorders who were treated with monotherapy atypical antipsychotics or augmentation therapy. However, methodological flaws of included studies may limit final conclusions of this review and larger placebo-controlled trials are warranted comparing standard treatment with monotherapy and augmentation therapy of atypical antipsychotics and placebo. In addition, higher dropout rates and side effects from treatment with atypical antipsychotics may limit the use of atypical antipsychotics in patients with anxiety disorders.

Role of the funding source

No limitations were made by any funding source regarding collection, management, analysis, or interpretations of the data. No government or industry sponsor participated in the interpretation or writing of this article, thus there were no limitations on the use of these data for publications or presentations.

Contributors

Authors Nienke Vulink and Damiaan Denys designed the study. Author Nienke Vulink performed the literature searches, undertook the statistical analysis and wrote the first draft of the manuscript. Author Martijn Figee and Damiaan Denys improved the first draft of the mamuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

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