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# Role and clinical implications of atypical antipsychotics in anxiety and related disorders: a systematized review

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| **Abstract:** | Introduction. Atypical antipsychotics (AAs) may have a role in the treatment of anxiety disorders. No reviews on their differential use in different anxiety disorders have been recently run. The aim of this systematized review was to select data on efficacy and comparative effectiveness of AAs as treatment of Anxiety Disorders, Obsessive-Compulsive Disorder, and Trauma-related Disorders in order to provide a guidance for clinicians on when and which AA use.<br>Methods. We searched on PubMed, Psychnet and Cochrane Libraries from inception to July 2015. Search results were limited to open-label and randomized controlled trials of adult patients.<br>Results. Our systematized search identified 1298 papers, of which 191 underwent full text review and 97 were included. Olanzapine, risperidone, and quetiapine XR have a role in the treatment of uncomplicated GAD; risperidone and aripiprazole seem effective in resistant OCD; risperidone and olanzapine in PTSD.<br>Conclusion. This systematized review supports the evidence that AAs are effective only in a minority of the off-label conditions in which they are currently used and that AAs are not all the same. Their use should be based on a balance between efficacy and side effects, and on the characteristics as well as the preference of the treated |

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| | patient. |

# U N I V E R S I T A' D I T O R I N O

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To the Editor-in-Chief

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Prof. Stuart A. Montgomery

RE: Submission of manuscript

We submit for publication as a review the manuscript "Role and clinical implications of atypical antipsychotics in anxiety and related disorders: a systematized review" (Authors: Umberto Albert, Claudia Carmassi, Fiammetta Cosci, David De Cori, Marco Di Nicola, Silvia Ferrari, Nicola Poloni, Ilaria Tarricone, Andrea Fiorillo). We reviewed the literature with the aim to select data on efficacy and comparative effectiveness (where possible) of AAs as treatment of Anxiety Disorders (Specific Phobia, Social Anxiety Disorder, Panic Disorder, Generalized Anxiety Disorder), Obsessive-Compulsive Disorder, Trauma-related Disorders (Acute and Post-Traumatic Stress Disorder), in order to provide a guidance for clinicians on when and which AA use. We will be honoured to have our paper published in International Clinical Psychopharmacology.

Waiting for your response, we thank you very much for your kind attention.

Yours truly, on behalf of all Authors

Umberto Albert


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# Role and clinical implications of atypical antipsychotics in anxiety and related disorders: a systematized review

[Running head: atypical antipsychotics in anxiety disorders]

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Abstract

Introduction. Atypical antipsychotics (AAs) may have a role in the treatment of anxiety disorders. No reviews on their differential use in different anxiety disorders have been recently run. The aim of this systematized review was to select data on efficacy and comparative effectiveness of AAs as treatment of Anxiety Disorders, Obsessive-Compulsive Disorder, and Trauma-related Disorders in order to provide a guidance for clinicians on when and which AA use.

Methods. We searched on PubMed, Psychnet and Cochrane Libraries from inception to July 2015. Search results were limited to open-label and randomized controlled trials of adult patients.

Results. Our systematized search identified 1298 papers, of which 191 underwent full text review and 97 were included. Olanzapine, risperidone, and quetiapine XR have a role in the treatment of uncomplicated GAD; risperidone and aripiprazole seem effective in resistant OCD; risperidone and olanzapine in PTSD.

Conclusion. This systematized review supports the evidence that AAs are effective only in a minority of the off-label conditions in which they are currently used and that AAs are not all the same. Their use should be based on a balance between efficacy and side effects, and on the characteristics as well as the preference of the treated patient.

Keywords: atypical antipsychotics, anxiety disorders, obsessive-compulsive disorder, posttraumatic stress disorder

Disclosure: The use of AAs in anxiety disorders is not approved by the FDA.

## Introduction

Atypical antipsychotic (AAs) medications are approved for the treatment of Schizophrenia, Bipolar Disorder and Major Depression under drug-specific circumstances. However, their use is rapidly increasing and their off-label prescription is, at least partially, responsible for their widespread use (Verdoux et al., 2010; Alexander et al., 2011; Comer et al., 2011; Gallini et al., 2013; Carton et al., 2015). It has been estimated that, among adults, off-label prescriptions represent 40 to 75% of all antipsychotic prescriptions (Carton et al., 2015). The main use is for mood disorders, anxiety disorders, insomnia and agitation. For instance, quetiapine is the most frequently prescribed off-label antipsychotic for anxiety, insomnia (Carton et al., 2015), and functional gastrointestinal disorders (FGIDs) (Pae et al., 2013). The increase in the observed off-label antipsychotic prescriptions may be due to the widespread and inappropriate marketing practice (Breier, 2011), the inadequate efficacy of first-line therapies, and the indications of the international guidelines. For instance, the National Institute of Clinical and Health Excellence (NICE) Guidelines suggests adding an antipsychotic to an SSRI or to clomipramine as first-line treatment strategy in adult patients with Obsessive-Compulsive Disorder (OCD) resistant to antidepressants (NICE 2006). However, antipsychotic drugs are generally recommended as a class, although they are not all the same differing at least in pharmacokinetic and pharmacodynamic profiles, and no advice is provided on how to use a specific antipsychotic for a specific disorder/symptom.

Anxiety disorders are a heterogeneous group of illnesses having different clinical presentations, ranging from relatively moderate symptoms to severe functional impairment and profound disability. Such heterogeneity has been recognized in DSM-5, which divided the DSM-IV chapter of anxiety disorders in three (more homogeneous) groups: Anxiety Disorders (Specific Phobia, Social Anxiety Disorder, Panic Disorder, Generalized Anxiety Disorder); Obsessive-Compulsive and Related Disorders; and Trauma and Stressor-Related Disorders (Acute and Posttraumatic Stress Disorder).

Anxiety disorders are also very often associated with FGIDs, with functional dyspepsia (FD) and irritable bowel syndrome (IBS) as the most common variants. Around one in four patients with FGIDs suffer because of anxiety disorders and the prevalence of anxiety disorder comorbidity increases in parallel with symptoms frequency and severity (Pinto-Sanchez et al., 2015). The use of atypical antipsychotics (AAs) is increasing, either alone or in augmentation strategy, also in this category of patients.

Given the generally recommendation of antipsychotic drugs as a class and the heterogeneity of anxiety disorders, which anxious disorder/symptom is best suited for antipsychotic therapy? Which atypical antipsychotic (AA) is an evidence-based treatment for specific anxiety disorders? Several reviews have been published on the use of AAs as a class in specific anxiety disorders (e.g. Depping et al., 2010; Komossa et al., 2010; Ahearn et al., 2011; Lalonde et al., 2011; Maher et al., 2011; Vulink et al., 2011; Han et al., 2014; Hershenberg et al., 2014; Wang et al., 2014), but no reviews on the differential use of AAs in different anxiety disorders have been recently run and several new placebo-controlled trials have been published in the last few years. In this framework, we reviewed the literature with the aim to select data on efficacy and comparative effectiveness (where possible) of AAs as treatment of Anxiety Disorders (Specific Phobia, Social Anxiety Disorder, Panic Disorder, Generalized Anxiety Disorder), Obsessive-Compulsive Disorder, Trauma-related Disorders (Acute and Post-Traumatic Stress Disorder), and FIGDs in order to provide a guidance for clinicians on when and which AA use.

## Methods

We searched on PubMed, Psychnet and Cochrane Libraries from inception to July 2015. Articles published in English and related to the use of AAs in anxiety disorders, OCD and trauma-related disorders were evaluated. The keyword “antipsychotic” was combined using the boolean AND with ”specific phobia”, “social phobia”, “social anxiety disorder”, “generalized anxiety disorder”, “obsessive-compulsive disorder”, “post-traumatic stress disorder”, “acute stress disorder”, “functional gastrointestinal disorder”. An additional search was performed combining ”specific phobia”, “social phobia”, “social anxiety disorder”, “generalized anxiety disorder”, “obsessive-compulsive disorder”, “post-traumatic stress disorder”, “acute stress disorder”, “functional gastrointestinal disorder” with “aripiprazole”, “olanzapine”, “quetiapine”, “paliperidone”, “risperidone”, “ziprasidone” via the Boolean AND. Finally, a manual search for reference lists from articles selected in the previous search and for any relevant reviews was done. Search results were limited to open-label trials and randomized controlled trials of adult patients.

## Results

Our systematized search identified 1298 papers, of which 191 articles underwent full text review and 97 papers were included; table 1 reports the number of articles selected and reviewed.

### *Second-generation antipsychotics in Specific Phobia*

Only one RCT examined the putative acute anxiolytic effect of a single dose of quetiapine XT during virtual reality exposure in patients with arachnophobia (Diemer et al., 2013). Overall, quetiapine showed significant anxiolytic effects, although these effects were not seen on the primary outcome measure (VAS Anxiety), but were limited to somatic anxiety symptoms.

### *Second-generation antipsychotics in Social Anxiety Disorder*

The efficacy of quetiapine as monotherapy in Social Anxiety Disorder (SAD) has been evaluated in three studies (Table 2). In an 8-week, randomized, double-blind, placebo-controlled study quetiapine failed to differentiate from placebo (Vaishnavi et al., 2007). The small size of the sample might have diminished the power of the study to detect differences between the two groups as 20% of the quetiapine patients versus none of those on placebo showed an improvement in SAD-related symptomatology. A second RCT tested the efficacy of the acute administration of a single dose of quetiapine (25 mg) versus placebo an hour before exposure to a 4-minute virtual reality public speaking challenge (Donahue et al., 2009) and no significant effect was found for quetiapine on any of the outcome measurements. Compared with placebo, quetiapine was significantly associated with higher heart rate and sleepiness. Notably, the authors could not determine whether higher or chronic doses would have been more effective in limiting social anxiety symptoms in response to the task. Quetiapine showed to be effective only in one open label study carried out with 13 patients (11 drug-naïve and 2 non-responders to an adequate dose of paroxetine) (Schutters et al., 2005).

Some data suggests effectiveness of olanzapine as monotherapy in SAD treatment (Barnett et al., 2002). In an 8-week, double-blind, placebo-controlled trial, an initial dose of olanzapine (5 mg/day), titrated up to a maximum of 20 mg/day, proved to be more effective than placebo. It is noteworthy that only 7 subject completed all 8 weeks of treatment, 4 from the olanzapine group and 3 from the placebo one, and that both olanzapine and placebo were associated with negligible weight gain.

Simon et al. (2006) performed an 8-week open-label trial using risperidone as augmentation therapy in 30 patients with Generalized Anxiety Disorder, Social Anxiety Disorder or Panic Disorder who had not previously responded to an adequate (or maximally tolerated) dose of an SSRI or a benzodiazepine during at least 8 weeks of treatment. Seven patients (23.3%) were diagnosed with SAD. Among them, risperidone augmentation led to a significant decrease in clinical symptomatology, as indicated by improved scores in the scales used for the outcome measurements.

*Second-generation antipsychotics in Panic Disorder (PD)*

The use of second-generation antipsychotics as monotherapy or adjunctive treatment in patients with panic disorder (PD) is under-studied (Table 3). To our knowledge, only one RCT, although single-blind, was run; subjects with a history of panic attacks were randomized to receive either risperidone or paroxetine in monotherapy: all subjects showed a reduction in both the frequency and severity of panic attacks regardless of treatment received (Prosser e al., 2009). To note that both patients with a diagnosis of PD and patients with a diagnosis of major depression with panic attacks were included; about 40% of patients under risperidone dropped out prematurely vs. about 60% of those under paroxetine; paroxetine was not titrated (the initial dose was 30 mg/day); and the group under paroxetine had a statistically significant higher severity of baseline depressive symptoms than those under risperidone (Prosser e al., 2009).

An open-label studiy evaluated the use of olnzapine monotherapy in treatment-resistant PD patients (Hollifield et al., 2005); they showed that 50% of the participants under olanzapine were panic free and 60% were free of anticipatory anxiety at the end of the trial. To note, Hollifield et al. (2005) studied only 10 subjects and no studies verified the effects of antipsychotic discontinuation.

Few studies evaluated the efficacy of second-generation antipsychotics as adjunctive treatment in PD patients: all of them were addressed to treatment-resistant subjects and no RCT was run. Hoge and colleagues (2008) evaluated the efficacy of aripiprazole addition in a mixed group of PD (n=10) and generalized anxiety disorder (GAD) patients. Sepede et al. (2006) assessed the effects of olanzapine in treatment-resistant patients: symptom improvement was observed from the second week already; in addition, the PD with agoraphobia group had a greater improvement than the PD group. To note that about 16% of the sample dropped out for side effects and that the authors did not verify the effects of

antipsychotic discontinuation. Similarly, Simon et al. (2006) showed positive effects of risperidone as add on treatment of PD patients under SSRI or serotonin and noradrenaline reuptake inhibitor (SNRI) and/or benzodiazepines. The sample was small (n = 7) and no information on antipsychotic discontinuation was provided. Finally, three case reports suggested the effects of olanzapine (Etxebeste et al., 2000; Khaldi et al., 2003; Chao 2004) as augmentation in treatment-resistant PD patients and one case report suggested to add quetiapine extending release to duloxetine (Pitchot and Ansseau, 2012).

Three RCTs evaluated the efficacy of risperidone monotherapy (mean dose 2.5 mg/day) (Sheehan et al., 2009), quetiapine XR monotherapy (mean dose 186.4 mg/day)(Sheehan et al., 2013) and ziprasidone monotherapy (mean dose 146.7 mg/day) (Suppes et al., 2014) in bipolar patients with comorbid panic symptoms or GAD; both risperidone and ziprasidone failed to differentiate from placebo, while quetiapine XR resulted in greater improvement than placebo and valproate.

### *Second-generation antipsychotics in Generalized Anxiety Disorder*

Evidence is available for the following AAs: aripiprazole (only 2 open label studies), olanzapine, quetiapine, quetiapine XR, risperidone and ziprasidone (Table 4).

Olanzapine (flexible dose) was used in augmentation in patients resistant to a 6-week treatment with fluoxetine 20 mg/die: it was superior to placebo on only 2 out of 4 outcome measures (responder rates based on Clinical Global Impression – Severity scale and Hamilton Anxiety Rating Scale scores), suggesting a potential benefit (Pollack et al., 2006). Four trials (3 double-blind and 1 open label studies) were identified for risperidone: only one (Sheehan et al., 2009) tested risperidone monotherapy but in bipolar patients with comorbid GAD and had negative results. The other three trials, two of which controlled versus placebo (Brawman-Mintzer et al., 2005; Pandina et al., 2007), were augmentation studies in resistant GAD: risperidone was more effective than placebo in only 1 double-blind study (Brawman-Mintzer et al., 2005) and in one open-label trial (Simon et al., 2006). Ziprasidone was tested in two 8-week, double-blind, placebo-controlled studies which gave negative results (ziprasidone = placebo): the first either as monotherapy and add-on treatment in resistant GAD (Lohoff et al., 2010) and the second as monotherapy in bipolar patients with comorbid panic or GAD (Suppes et al., 2014).

Quetiapine is by far the most extensively studied antipsychotic in GAD, with 13 trials, 9 of which with quetiapine extended-release (XR). Quetiapine XR was studied as add-on treatment in resistant

GAD in 2 double-blind trials of which one had negative results (Simon et al., 2008) and one had positive results in two out of four outcome measures (Altamura et al., 2011). Quetiapine XR was also studied in 2 open label studies which showed its efficacy (Adson et al., 2004; Katzman et al., 2008). However, the study by Adson (2004) included patients suffering from depression, panic disorder, and specific phobia beyond GAD. Quetiapine XR was prevalently studied in monotherapy (7 out of 9 trials), and was generally effective (5 positive RCTs in primary, uncomplicated GAD and 1 positive RCT in bipolar patients with comorbid GAD). Dosages were comprised between 50 to 300 mg/day (in only one research, up to 400 mg/day), and most studies lasted 8-12 weeks, though a maintenance study included follow-up at 52 weeks (Katzman et al., 2011). More details are included in table 4.

No studies directly compared AAs for treating GAD: quetiapine XR monotherapy was compared to paroxetine 20 mg/die (Bandelow et al., 2010) and escitalopram 10 mg/die (Merideth et al., 2012) under double-blind conditions, and to a placebo arm in uncomplicated GAD. The results show that quetiapine XR was as effective as the comparators, with fewer sexual side effects than paroxetine.

### *Second-generation antipsychotics in Obsessive-Compulsive Disorder*

Several randomized, double-blind, placebo-controlled studies exist supporting the use of antipsychotic addition to Serotonin Reuptake Inhibitors (SRIs) in resistant OCD; however, the use of antipsychotics in monotherapy either in drug-naïve or resistant patients has never been studied under double-blind conditions. In addition, atypical antipsychotics seem better tolerated in the short-term but less in the long-term due to metabolic side effects (Albert et al., 2013).

Concerning the efficacy of adding second-generation antipsychotics, 6 RCTs examined the addition of quetiapine (Atmaca et al. 2002 – single-blind - Denys et al., 2004; Carey et al., 2005; Fineberg et al., 2005; Kordon et al., 2008; Diniz et al., 2011), 3 examined the addition of risperidone (McDougle et al., 2000; Hollander et al., 2003; Erzegovesi et al., 2005), 2 examined the addition of olanzapine (Bystritsky et al., 2004; Shapira et al., 2004) and aripiprazole (Muscatello et al., 2011; Sayyah et al. 2012), and 1 examined the addition of paliperidone (Storch et al. 2013). Their results are summarized in Table 5. Risperidone and aripiprazole both differentiated from placebo in all studies and were considered effective. No evidence could be identified for the efficacy of adjunctive quetiapine (no difference in response between quetiapine and placebo in four of the five double-blind studies) and olanzapine (one

positive – Bystritsky et al., 2004 – and one negative study – Shapira et al., 2004). However, the negative study with olanzapine (Shapira et al., 2004) might have been biased by the fact that patients not responding to 8 weeks of SRI monotherapy (instead of the usual 12 weeks used to show response) were included. The paliperidone negative study (Storch et al., 2013) suffered from the same bias: the duration of treatment was only 8 weeks at a medium-to-high dose. Paliperidone did not differentiate from placebo, and its administration resulted in significant baseline to post-treatment reductions in obsessive-compulsive symptoms (-7.98 points in Yale-Brown Obsessive-Compulsive Scale - YBOCS score); placebo administration also resulted in medium size, trend-level significant YBOCS changes (-4.02 points).

Only 3 studies compared effectiveness of antipsychotics in OCD (Li et al., 2005; Maina et al., 2008; Selvi et al., 2011). The first compared risperidone and haloperidol addition (Li et al., 2005): both risperidone and haloperidol significantly reduced obsessions when compared with placebo, and there was a tendency for haloperidol, and to a lesser degree for risperidone, of reducing compulsion and YBOCS total scores. However, 40% of patients terminated haloperidol treatment early due to intolerable side effects, versus none in the risperidone phase. Maina and colleagues (2008) directly compared, in a single-blind study, risperidone and olanzapine addition to SRIs in resistant OCD patients: the two compounds resulted equally effective in improving obsessive-compulsive symptoms. Finally, Selvi and coworkers (2011) compared risperidone and aripiprazole augmentation: both drugs proved to be effective strategies in resistant patients although a significantly higher response rate was found with risperidone (72.2%) compared to aripiprazole (50%).

The efficacy of the combination of SRIs and antipsychotic from the beginning of treatment, in non-refractory OCD patients was examined in one study only (Vulink et al., 2009): the combination of quetiapine (300-450 mg) and citalopram (60 mg) was more effective than citalopram alone.

At present, it is uncertain how long adjunctive antipsychotic treatment should be maintained. The discontinuation of the antipsychotic in patients previously responsive only to the augmentation strategy leads to an exacerbation of obsessive-compulsive symptoms in the vast majority of patients (83.3% within the 24-week follow-up) (Maina et al., 2003). However, if such a treatment is carried out over the long term, patients are exposed to the common and serious adverse effects associated with long-term antipsychotic administration, especially the metabolic ones (Matsunaga et al., 2009). Indeed, the

metabolic syndrome is associated with the duration of the exposure (lifetime) to antipsychotics and is present in about a quarter of treated patients (Albert et al., 2013).

### *Second-generation antipsychotics in Post-Traumatic Stress Disorder (PTSD) and Acute Stress Disorder*

Several randomized, double-blind, placebo-controlled trials support the use of antipsychotic addition or monotherapy in resistant PTSD patients. Open-label studies also support the use of some AAs in PTSD. The most studied antipsychotic agent is risperidone; it was first investigated in veterans with chronic psychotic PTSD, showing an effect in improving intrusive and psychotic symptoms, aggressive behaviors and the overall PTSD symptomatology (Hamner et al., 2003; Monnelly et al., 2003; Reich et al., 2004; Bartzokis et al., 2005; Padala et al., 2006). Hamner et al. (2003) first showed that risperidone is superior to placebo as adjunctive treatment in 40 subjects with combat psychotic chronic PTSD. Monnelly et al. (2003) confirmed these data highlighting an improvement in irritability and intrusive thoughts. In 2005, Bartzokis and colleagues reported results on a larger sample of 65 veterans with combat PTSD, where risperidone significantly improved response to ongoing treatment with SSRIs. However, two more recent trials did not report a significant improvement in PTSD symptomatology both in civilians (Rothbaum et al., 2008) and veterans (Krystal et al., 2011) with PTSD. Of note, in the Rothbaum study both groups, the riperidone addition and the placebo one, improved over the course of the treatment, and then risperidone failed to show a superiority over placebo. In the Krystal study, subjects included were refractory, that is not responding to ≥2 SRI trials, and this might explain the lack of effectiveness. Fewer studies explored risperidone efficacy among women with chronic PTSD due to either childhood abuse or sexual and domestic abuse, but all showed a significant improvement in reducing PTSD symptoms, particularly intrusive and hyperarousal one (Reich et al., 2004; Padala et al., 2006).

Olanzapine has also been tested in a few randomized placebo-controlled studies (Butterfield et al., 2001; Stein et al., 2002; Carey et al., 2012). In a first double-blind trial on 15 patients, it did not seem to have significant effects with respect to placebo (Butterfield et al., 2001). Conversely, Stein et al. (2002) reported a significant reduction in the overall PTSD symptoms, particularly sleep disturbances, in 19 veterans with chronic PTSD with adjunctive olanzapine to an on-going SSRI. More recently, the first

study to report controlled evidence of the efficacy of olanzapine monotherapy in an exclusively non-combat related chronic PTSD group, reported this to be superior to placebo (Carey et al., 2012).

Quetiapine and aripiprazole have also been studied in PTSD, although no double-blind placebo-controlled studies exist; for ziprasidone only data from an incomplete study are available (Kellner et al., 2010). A daily dose of quetiapine ranging between 25 to 300/400 mg was associated with a significant reduction in posttraumatic stress symptomatology in veterans with combat PTSD, either as adjunctive treatment or monotherapy (Ahearn et al., 2006; Hamner et al., 2003; Kozaric-Kovacic and Pivac, 2007). Although these results are encouraging, no placebo controlled trial has yet been conducted with quetiapine for PTSD patients, and the only retrospective cohort study available on 247 veterans with PTSD showed prazosin to be superior over quetiapine in the long-term treatment of nightmares and sleep disturbances (Byers et al., 2010). Several open-label monotherapy and adjunctive treatment studies suggest a potential effectiveness of aripiprazole in PTSD (Villareal et al., 2007; Mello et al., 2008; Robert et al., 2009; Youssef et al., 2012). However, preliminary data from the first randomized placebo-controlled trial on 16 veterans with chronic PTSD failed to confirm adjunctive aripiprazole efficacy over placebo (although aripiprazole outperformed placebo on several items of the Clinician-Administered PTSD Scale) (Naylor et al., 2015).

Scant data have been reported for the treatment of symptoms of acute stress disorder with AAs: no randomized placebo controlled study has been conducted and only reports on a few cases are available. In particular, Eidelman et al. (2000) reported the possible benefit of risperidone on 4 cases where flashbacks were reported in patients hospitalized for the treatment of physical trauma.

### *Second-generation antipsychotics in somatisation and FGIDs*

Some AAs have been studied as augmentation treatments in somatoform disorders: paliperidone 3 mg/day added to citalopram 20 mg/day was more effective than citalopram alone in a 6-week, randomized study (Huang et al., 2012). Aripiprazole (6-18 mg/day) was added to fluvoxamine (300 mg/day) and paroxetine (50 mg/day) in 2 patients with somatoform disorder who had an inadequate response to SSRI; signs of improvement were observed within 2-4 weeks, and symptoms disappeared without any adverse effects 8 weeks later (Nagoshi et al., 2014). Atypical antipsychotics can be beneficial in lower dosages for patients with FGIDs because of their analgesic properties (alone or in synergism

with antidepressants) (Fishbain et a., 2004) and of their sedative and anxiolytic effects. However, only 1 open label clinical studies with AAs as augmentation treatment for resistant FGIDs could be retrieved. Grover et al. (2009) reported on the effectiveness of adding low-dose quetiapine (25–100 mg) to antidepressants in patients with severe Irritable Bowel Syndrome and functional abdominal pain syndrome, not responding to antidepressant monotherapy.

### Summary of findings and discussion

Atypical antipsychotics may have a role in the treatment of anxiety disorders (Stein and Steckler, 2010). The aim of the present paper was to review the literature on efficacy and comparative effectiveness of AAs in Anxiety Disorders, Obsessive-Compulsive Disorder, and Trauma-related Disorders in adults, in order to provide an evidence-based guidance for clinicians on when and how to use AAs in these clinical conditions. Moreover, we added a specific paragraph on the use of AAs in functional gastrointestinal disorders (FGIDs), based on our belief that anxiety disorders and FGIDs are correlated clinical conditions and that AAs will be studied in the future in these functional disorders. FGIDs are often considered at the "functional" end of the "functional-organic" spectrum where a disorder is characterized by the absence of detectable structural abnormalities using traditional diagnostic techniques, such as endoscopy or imaging (Grover & Drossman, 2011). FGIDs can be conceptualized with a biopsychosocial construct where an influence of central nervous system at spinal and supraspinal levels results in sensory and motor dysfunctions of the GI tract (Drossman, 2003). The trigger can be peripheral (e.g., GI infection, abdominal surgery) or central (e.g., a history of major stressful life events, such as sexual abuse, separation, and personal losses), but psychosocial factors often play an important role in perpetuation and clinical manifestation of this disorder through centrally mediated pathways (Drossman et al., 1996; Grover and Drossman, 2011).

This systematized review supports the evidence that atypical antipsychotics are effective only in a minority of the off-label conditions in which they are currently used and that AAs are not all the same. Only some of the investigated AAs demonstrated efficacy under double-blind conditions; only some AAs are effective in specific disorders. Clinicians should then discriminate between AAs and prescribe off-label specific molecules for specific mental disorders.

We summarise below the main recommendations we can derive from the literature reviewed:

*1. Social Anxiety Disorder and Panic Disorder*: No conclusions can be drawn regarding the effectiveness of AAs.

2. *Generalized Anxiety Disorder.* Results from double-blind studies suggest that olanzapine and risperidone might be effective as add-on treatments in GAD-resistant patients; open label studies suggest that aripiprazole add-on may be effective in resistant patients, but more trials (placebo-controlled) are needed. Ziprasidone is not more effective than placebo in resistant GAD. On the contrary, quetiapine XR monotherapy seems effective for uncomplicated GAD, but issues of adverse effects and tolerability may limit its use (Hershenberg et al., 2014). Relatively low doses of XR 150 mg/day consistently outperformed higher XR 300 mg/day doses, and initiating at 50 mg might be sufficient to produce benefit (Hershenberg et al., 2014).

*4. Obsessive-Compulsive Disorder.* Several randomized, double-blind, placebo-controlled studies support the use of antipsychotic addition to SRIs in treatment-resistant OCD (Albert et al., 2014). Risperidone and aripiprazole both differentiated from placebo and may be considered effective, while no evidence could be identified for the efficacy of adjunctive quetiapine. Efficacy of olanzapine add-on is controversial although potential biases of one of the 2 studies that evaluated its efficacy. Data on paliperidone should be considered preliminary. In brief, risperidone or aripiprazole addition to SRIs in patients not responding to at least 12 weeks at a medium-to-high SRI dose seems effective. Given the strength of the evidence, we do suggest this option especially in patients who showed a partial but unsatisfactory response. An alternative evidence-based strategy is the addition of CBT to pharmacotherapy (Albert and Bogetto 2015), given its superior efficacy and less negative adverse effect profile compared to antipsychotics (Simpson et al., 2013).

*5. Post-Traumatic Stress Disorder*. Several studies have explored the efficacy of AAs in PTSD, including RCTs, particularly when chronic and associated to co-occurring psychotic symptoms. Risperidone alone or as adjunctive treatment seems to be effective, mainly in resistant patients, at doses ranging between 2.0 and 2.5 mg/day. Olanzapine may be considered effective, based on positive results from RCTs and open-label studies. The efficacy of risperidone and olanzapine, although not confirmed in all studies, is both on global PTSD symptoms and individual PTSD symptoms' clusters, particularly intrusion, compared with placebo (Pae et al., 2008; Han et al., 2014). Aripiprazole and quetiapine might be beneficial, although controlled studies are needed before their use could be considered evidence-based;

aripiprazole showed no efficacy in the only RCT performed to date (Naylor et al., 2015) while open-label reports suggest both aripiprazole and quetiapine as effective.

*6. Somatoform and Functional Gastro-Intestinal Disorders.* Too few studies are available to come up with any conclusion about the effectiveness of AAs.

The present review of the literature has some limitations. First, several of the included studies had an open-label design without a control group. This limited our ability to draw conclusions for some of the anxiety disorders investigated. It is also possible that the efficacy of AAs in these open label trials could be overestimated. Second, most studies had small sample sizes; however we preferred to include them in order to have a preliminary idea of the findings currently available. Third, we included studies performed in the different populations (e.g., some of the trials included bipolar patients with comorbid panic/GAD or mixed samples of PD and MDD+PD patients); however we wanted to draw conclusions useful for the clinical practice where the presence of comorbidity is the rule. Fourth, the vast majority of the studies had relatively short durations; thus, they do not provide information on the long-term efficacy and tolerability of AAs.

Notwithstanding these limitations, olanzapine, risperidone, and quetiapine XR have a role in the treatment of uncomplicated GAD; risperidone and aripiprazole seem effective in resistant OCD; risperidone and olanzapine in PTSD (see Table 7 for a summary of results of double-blind studies in primary disorders). Their use should be, however, based on a balance between efficacy and side effects, and on the characteristics as well as the preference of the treated patient.

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Table(s)

Table 1 – Study flowchart

| | Total number of search results | Selected (full texts | Included in the review |
|---|---|---|---|
| Specific Phobia | 19 | 1 | 1 |
| Social Anxiety Disorder | 229 | 16 | 7 |
| Panic Disorder | 184 | 29 | 12 |
| Generalized Anxiety Disorder | 208 | 30 | 23 |
| Obsessive-Compulsive Disorder | 311 | 59 | 24 |
| Post-Traumatic Stress Disorder | 283 | 50 | 28 |
| Acute Stress Disorder | 64 | 6 | 2 |
| Total | 1298 | 191 | 97 |

Table 2 - Second-generation antipsychotic use in Social Anxiety Disorder

| Antipsychotic | Authors | Sample (N) | Trial duration (weeks) | Dose (mg/die) | Mean dose (mg/die) | Monotherapy (M) or Augmentation (A) | Relevant notes | Results |
|---|---|---|---|---|---|---|---|---|
| Olanzapine | Barnett et al. 2002* | 12 | 8 | 5-20 | 12.3 ± 6.5 | M | | Olanzapine>Placebo |
| Quetiapine | Schutters et al. 2005+ | 13 | 12 | 150-300 | 250±54 | M | | Effective |
| | Vaishnavi et al. 2007* | 15 | 8 | 50-400 | 147±105 | M | | Quetiapine=Placebo |
| | Donahue et al. 2009* | 20 | // | 25 (fixed-dose) | 25 (fixed-dose) | M | acute impact of a single dose of quetiapine versus placebo after SAD-relevant virtual anxiety cue exposure | Quetiapine=Placebo |
| Risperidone | Simon et al. 2006+ | 7 | 8 | 0.25-3 | 1.12 ± 0.68 | A | Resistant patients | Effective |

+ open label

* double-blind, placebo-controlled

Table 3 - Second-generation antipsychotic use in Panic Disorder

| Antipsychotic | Authors | Sample (N) | Trial duration (weeks) | Dose (mg/die) | Mean dose (mg/die) | Monotherapy (M) or Augmentation (A) | Relevant notes | Results |
|---|---|---|---|---|---|---|---|---|
| Aripiprazole | Hoge et al. 2008+ | 10 | 8 | 2.5-30 | 10.5±4.9 | A | Resistant patients | Effective |
| Olanzapine | Hollifield et al. 2005+ | 10 | 8 | 2.5-20 | 12.3±6.5 | M | Resistant patients | Effective |
| | Sepede et al. 2006+ | 31 | 12 | 5 (fixed-dose) | 5 (fixed-dose) | A | Resistant patients | Effective (more in PD + AGO than in PD) |
| Quetiapine XR | Sheehan et al. 2013*** | 149 | 8 | 50-300 | 186 | M | Bipolar patients with comorbid panic or GAD | Quetiapine XR>placebo |
| Risperidone | Simon et al. 2006+ | 7 | 8 | 0.25-3.00 | 1.12±0.68 | A | Resistant patients | Effective |
| | Prosser et al. 2009** | 55 | 8 | 0.125-1.0 | 0.53 | M | PD and MDD + panic attacks | Risperidone=Paroxetine |
| | Sheehan et al. 2009 * | 111 | 8 | 0.5-4 | 2.5±1.1 | M | Bipolar patients with comorbid panic or GAD | Risperidone=placebo |
| Ziprasidone | Suppes et al. 2014 * | 49 | 8 | 40-160 | 146.7±20.7 | M | Bipolar patients with comorbid panic or GAD | Ziprasidone=placebo |

[+] open label

* double-blind, placebo-controlled

[**] single blind, active drug as comparator

*** double-blind, placebo and active-comparator controlled

Table 4 - Second-generation antipsychotic use in Generalized Anxiety Disorder

| Antipsychotic | Authors | Sample (N) | Trial duration (weeks) | Dose (mg/day) | Mean dose (mg/die) | Monotherapy (M) or Augmentation (A) | Relevant notes | Results |
|---|---|---|---|---|---|---|---|---|
| Aripiprazolo | Menza et al. 2007+ | 9 | 6 | ≥10 | 13.9 | A | Resistant patients | Effective |
| | Hoge et al. 2008+ | 13 | 8 | 2.5-30 | 10.5±4.9 | A | Resistant patients | Effective |
| Olanzapine | Pollack et al. 2006 * | 24 | 6 | 2.5-20 | 8.7±7.1 | A | Resistant patients | Olanzapine>placebo on 2/4 outcome measures |
| Quetiapine | Adson et al. 2004+ | 11 | 9 | 25-300 | 180 | A | Not only GAD patients | Effective |
| | Katzman et al. 2008+ | 40 | 12 | 25-800 | 386 | A | Resistant patients | Effective |
| | Simon et al. 2008* | 22 | 8 | 25-400 | 120.5±100.5 | A | Resistant patients | Quetiapine=placebo |
| | Altamura et al. 2011** | 20 | 8 | 25-150 | 50 | A | Resistant patients | Quetiapine>placebo on 2/4 outcome measures |
| Quetiapine XR | Bandelow et al. 2010*** | 873 | 10 | 50 | Fixed-dose | M | | Quetiapine XR>placebo |
| | | | | 150 | | | | Quetiapine XR>placebo |
| | Katzman et al. 2011* | 432 | 52 | 50-300 | 162.8±88.3 | M | | Quetiapine XR>placebo |
| | Khan et al. 2011* | 951 | 10 | 50 | Fixed-dose | M | | Quetiapine XR>placebo |
| | | | | 150 | | | | Quetiapine XR>placebo |
| | | | | 300 | | | | Quetiapine XR=placebo |
| | Merideth et al. 2012*** | 854 | 10 | 150 | Fixed-dose | M | | Quetiapine XR>placebo |
| | | | | 300 | | | | Quetiapine XR>placebo |
| | Mezhebovsky et al. 2013* | 450 | 11 | 50-300 | 167.6±62.7 | M | Elderly (> 66 yo) | Quetiapine XR>placebo |
| | Sheehan et al. 2013*** | 149 | 8 | 50-300 | 186 | M | Bipolar patients with comorbid panic or GAD | Quetiapine XR>placebo |
| | Gao et al. 2014* | 100 | 8 | 50-300 | 276±50 | M or A to a mood stabilizer | Bipolar depressed with comorbid GAD and other disorders | Quetiapine XR=placebo |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gabriel 2011+ | 24 | 12 | 50-400 | - | A | Resistant patients | Effective |
| | Khan et al. 2014* | 409 | 8 | 50-300 | - | A | Resistant patients | Quetiapine XR=placebo |
| Risperidone | Sheehan et al. 2009 * | 111 | 8 | 0.5-4 | 2.5±1.1 | M | Bipolar patients with comorbid panic or GAD | Risperidone=placebo |
| | Brawman-Mintzer et al. 2005 * | 40 | 5 | 0.5-1.5 | 1.1±0.4 | A | Resistant patients | Risperidone>placebo |
| | Simon et al. 2006+ | 16 | 8 | 0.25-3.00 | 1.12±0.68 | A | Resistant patients | Effective |
| | Pandina et al. 2007* | 417 | 4 | 0.25-2 | | A | Resistant patients | Risperidone=placebo |
| Ziprasidone | Snyderman et al. 2005+ | 13 | 7 | 20-80 | 40 | M | Resistant patients | Effective |
| | Lohoff et al. 2010 * | 62 | 8 | 20-80 | 50.2 | M | Resistant patients | Ziprasidone=placebo |
| | | | | | | A | | Ziprasidone=placebo |
| | Suppes et al. 2014 * | 49 | 8 | 40-160 | 146.7±20.7 | M | Bipolar patients with comorbid panic or GAD | Ziprasidone=placebo |

[+] open label

* double-blind, placebo-controlled

** single-blind, placebo-controlled

*** double-blind, placebo and active-comparator controlled

Table 5 - Efficacy of antipsychotic augmentation in treatment-resistant OCD: double-blind, placebo-controlled studies

| Antipsychotic | Authors | Sample (N) | Trial duration (weeks) | Dose (mg/die) | Mean dose (mg/die) | Minimal length of SRI treatment before enrollment in the study | Results |
|---|---|---|---|---|---|---|---|
| Risperidone | McDougle et al. 2000 | 36 | 6 | 1-6 | 2.2±0.7 | 12 | Risperidone>Placebo |
| | Hollander et al. 2003 | 16 | 8 | 0.5-3 | 2.25±0.86 | 12 | Risperidone>Placebo |
| | Erzegovesi et al. 2005 | 20 | 6 | 0.5 (fixed-dose) | 0.5 (fixed-dose) | 12 | Risperidone>Placebo |
| Olanzapine | Bystritsky et al. 2004 | 26 | 6 | 5-20 | 11.2±6.5 | 12 | Olanzapine>Placebo |
| | Shapira et al. 2004 | 44 | 6 | 5-10 | 6.1±2.1 | 8 | Olanzapine=Plabebo (patients in both arms improved) |
| Quetiapine | Atmaca et al. 2002** | 27 | 8 | 50-200 | 91±41 | 12 | Quetiapine>Placebo |
| | Denys et al. 2004 | 40 | 8 | 100-300 | 200 | 8 | Quetiapine>Placebo |
| | Carey et al. 2005 | 42 | 6 | 25-300 | 168.8±120.8 | 12 | Quetiapine=Placebo |
| | Fineberg et al. 2005 | 21 | 16 | 50-400 | 215±124 | 12 | Quetiapine=Placebo |
| | Kordon et al. 2008 | 40 | 12 | 400-600 | - | 12 | Quetiapine=Placebo |
| | Diniz et al. 2011# | 54 | 12 | 50-200 | 142±65 | 8 | Quetiapine<Placebo |
| Aripiprazole | Muscatello et al. 2011 | 40 | 16 | 15 (fixed-dose) | 15 (fixed-dose) | 12 | Aripiprazole>Placebo |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Sayyah et al. 2012 | 39 | 12 | 10 (fixed-dose) | 10 (fixed-dose) | 12 | Aripiprazole>Placebo |
| Paliperidone | Storch et al. 2013 | 34 | 8 | 3-9 | 4.94 | 8 | Paliperidone=Placebo<br>(patients in both arms improved) |

** single-blind, placebo-controlled study # double-blind, placebo or clomipramine controlled study

Table 6 - Second-generation antipsychotic use in Posttraumatic Stress Disorder

| Antipsychotic | Authors | Sample (N) | Trial duration (weeks) | Dose (mg/day) | Mean dose (mg/die) | Monotherapy (M) or Augmentation (A) | Relevant notes | Results |
|---|---|---|---|---|---|---|---|---|
| Aripiprazolo | Villarreal et al. 2007+ | 22 | 12 | 5-30 | 12.95 | M | | Effective |
| | Mello et al. 2008+ | 32 | 16 | 3.75-15 | 9.6±4.3 | M | | Effective |
| | Youssef et al. 2012+ | 10 | 12 | 5-30 | 21.5 | M | | Effective |
| | Robert et al. 2009+ | 17 | 12 | - | 13.06±6.45 | A | Resistant patients | Effective |
| | Naylor et al., 2015* | 16 | 10 | 5-20 | 10.0 | A | Resistant patients | Aripiprazole=placebo |
| Olanzapine | Petty et al. 2001+ | 48 | 8 | 5-20 | 14 | M | 40/48 Resistant patients | Effective |
| | Butterfield et al. 2001* | 15 | 10 | 5-20 | 14.1 | M | | Olanzapine=Placebo |
| | Carey et al. 2012* | 28 | 8 | 5-15 | - | M | | Olanzapine>Placebo |
| | Pivac et al. 2004+ | 55 | 6 | 5-10 | - | M | Resistant, psychotic patients | Olanzapine>Fluphenazine |
| | Stein et al. 2002* | 19 | 8 | 10-20 | 15.00±5.25 | A | Resistant patients | Olanzapine>Placebo |
| Quetiapine | Kozaric-Kovacic & Pivac 2007+ | 53 | 8 | 25-400 | 335.7±85.3 | M | Resistant, psychotic patients | Effective |
| | Hamner et al. 2003+ | 20 | 6 | 25-300 | 100±70 | A | Resistant patients | Effective |
| | Ahearn et al. 2006+ | 15 | 8 | 100-400 | 216 | A | Resistant patients | Effective |
| Risperidone | Kozarić-Kovacić et al. 2005+ | 26 | 6 | 2-4 | | M | Resistant, psychotic patients | Effective |
| | Padala et al. 2006* | 20 | 12 | 1-6 | 2.62 | M | | Risperidone>Placebo |
| | Hamner et al. 2003* | 40 | 5 | 1-5 | 2.5±1.25 | A | Resistant patients | Risperidone>Placebo |
| | Monnelly et al. 2003* | 15 | 6 | 0.5-2 | 0.57±0.13 | A | | Risperidone>Placebo on 3/8 outcome measures |
| | David et al. 2004+ | 17 | 12 | 1-3 | 2.3±0.6 | A | Resistant patients | Effective |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Reich et al. 2004* | 19 | 8 | 0.5-8 | 1.41 | A | | Risperidone>Placebo |
| Bartzokis et al. 2005* | 65 | 16 | 1-3 | - | A | | Risperidone>Placebo |
| Rothbaum et al. 2008* | 25 | 8 | - | 2.1 | A | Resistant patients | Risperidone=Placebo (both improved) |
| Krystall et al 2011* | 267 | 24 | 0.5-4 | 2.74 | A | Refractory patients (≥2 SRIs) | Risperidone=Placebo |

[+] open label

* double-blind, placebo-controlled

Table 7 - Summary of results from double-blind studies only (only studies on primary disorders are considered)

| Antipsychotic | Social Anxiety Disorder | Panic Disorder | Generalized Anxiety Disorder | Obsessive-Compulsive Disorder | Posttraumatic Stress Disorder |
|---|---|---|---|---|---|
| Aripiprazole | | | | | |
| Monotherapy | | | | | |
| Adjunctive | | | | 2 positive | 1 negative |
| Olanzapine | | | | | |
| Monotherapy | 1 positive | | | | 1 positive |
| | | | | | 1 negative |
| Adjunctive | | | 1 positive | 1 positive | 1 positive |
| | | | | 1 negative | |
| Quetiapine | | | | | |
| Monotherapy | 2 negative | | | | |
| Adjunctive | | | 1 positive (2/4 measures) | 1 positive | |
| | | | 1 negative | 4 negative | |
| Quetiapine XR | | | | | |
| Monotherapy | | | 5 positive | | |
| Adjunctive | | | 1 negative | | |
| Paliperidone | | | | | |
| Monotherapy | | | | | |
| Adjunctive | | | | 1 negative | |
| Risperidone | | | | | |
| Monotherapy | | | | | 1 positive |
| Adjunctive | | | 1 positive | 3 positive | 4 positive |
| | | | 1 negative | | 2 negative |
| Ziprasidone | | | | | |

| | |
|---|---|
| Monotherapy | 1 negative |
| Adjunctive | 1 negative |