REVIEW ARTICLE

Off-Label Use of Second Generation Antipsychotics in Anxiety Disorders and Obsessive Compulsive Disorder

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Abstract

There is a paucity of data to support „next-step" treatments for the many patients with anxiety disorders who remain symptomatic after initial pharmacotherapy. Because of their somewhat improved safety profile, second generation antipsychotics (SGAs) are increasingly used for the treatment of nonpsychotic anxiety. The published literature describing the efficacy of SGAs in patients with anxiety disorders is briefly reviewed, and the efficacy and safety of second generation antipsychotics in these patients is discussed. The literature reviewed was primarily comprised of small open-label trials, thus making it difficult to draw definitive conclusions. There is moderately strong controlled evidence supporting the use of some SGAs, either as adjunctive treatment or monotherapy, in the treatment of anxiety disorders. Despite the limitations of the trials reviewed, atypical antipsychotics represent a promising treatment modality when considering their improved side effect profile compared to conventional agents. The facts to date does not warrant the use of SGAs as first-line monotherapy or as first – adjunctive therapy in the treatment of anxiety disorders. Nevertheless, some patients with highly refractory anxiety disorders may benefit from the judicious and carefully monitored use of adjunctive SGAs. A careful risk-benefit assessment, on a case-by-case basis, must be undertaken by the physician.

INTRODUCTION

Primary treatment of anxiety disorders and obsessive-compulsive disorder (OCD) may be pharmacotherapeutic (particularly antidepressants) or psychotherapy (especially cognitive-behavioral techniques). Because many patiens appear to be resistant to treatment, it is important to consider augmentation of their management by other approaches. One of the most frequently used practices is to add one of the second generation antipsychotics (SGA). SGA are sometimes used in disorders for which they are not approved by regulatory authorities, but their use for these unapproved indications may represent a significant help to patiens. Such use is based on clinical experience, case reports, recommendations of experts, and open trials. Some SGA have antidepressant and sedative effects that could be involved in their mechanisms of action in anxiety disorders.

Addition of first generation antipsychotics (FGA) carries increased risk of akathisia in short-term and tardive dyskinesia in long-term administration. Therefore, FGA are reserved for situations where antidepressants or benzodiazepines do not have sufficient

effect or are contraindicated. SGA have averse effects on glucose and lipid metabolism, increase body weight, serum triglycerides and cholesterol. They also elicit insulin resistance, and treatment emergent CASE of diabetes heve been reported. Clozapine and olanzapine are particularly prone to these metabolic averse effects. Nevertheless, SGA are much safer than FGA in terms of motor side effects and thus are easier to tolerate. Therefore, SGA are one of the options in treatment resistant patients with panic disorder, social phobia, generalized anxiety disorder (GAD), (OCD) and posttraumatic stress disorder (PTSD) (Seifertová *et al* 2008).

PANIC DISORDER

Panic disorder is a common and disabling psychiatric disorder. Despite treatment advances, refractory panic disorder requires novel interventions. A large proportion of patients with panic attacks receiving approved pharmacotherapy do not respond or respond poorly to medication, it is important to identify additional therapeutic strategies for the management of panic symptoms. Clinical trials indicate that 20–40% of patients treated according to standard procedures remain symptomatic (Bandellow *et al* 2004). If the patient is resistant to the treatment of first choice (usually Selective Serotonine Reuptake Inhibitors (SSRIs), imipramine, clomipramine, Serotonine-Norephinefrine Reuptake Inhibitors (SNRI), or MonoAminOxidase Inhibitors (MAOIs), augmentation treatment is called for. A common strategy is to add a highly potent benzodiazepine. Preliminary findings suggest that the addition of drugs such as valproate, gabapentin, β-blockers and buspirone may enhance the effectiveness of the original drug (Gastfriend & Rosenbaum 1989). Other recommended medications for augmentation are bupropion, lithium, and low-dose chlorprothixene or SGA – olanzapine in 5–12,5 mg dose (Etxebeste *et al* 2000; Khaldi *et al* 2003; Chao 2004).

Ten people with refractory DSM-IV diagnosed panic disorder completed an 8-week, open-label, flexible-dose clinical trial (Hollifield *et al* 2005). Baseline, in-treatment, and end-of-treatment data for panic attacks, anticipatory anxiety, phobic avoidance, and impairment were collected. Refractory panic disorder patients required a wide dose range averaging 12.3 mg/day of olanzapine to significantly improve or ablate panic attacks. On the average, number of attacks decreased from 6.1/week at baseline to 1.1/week at the end of treatment, and anticipatory anxiety from 32% of the day to 8% of the day. At treatment end, 5 of 10 participants (50%) were panic free, 4 (40%) had one attack in the previous week, 1 (10%) had seven attacks in the previous week, and 6 of 10 participants (60%) were anticipatory anxiety free. There were also statistically and clinically significant improvements in impairment over the course of the trial. There were no significant changes in vital signs, emergent side effects, or aver-

age weight, although 6 of 10 people did gain weight. Authors concluded that olanzapine is potentially effective and safe in panic disorder.

Sepede *et al* (2006) evaluated the efficacy and tolerability of low-dose olanzapine augmentation in SSRIs-resistant panic disorder (PD) with or without agoraphobia. In this 12-week, open-label study, 31 adult outpatients with treatment-resistant PD who had previously failed to respond to SSRI treatment were treated with fixed dose of olanzapine (5 mg/d) in addition to SSRI. Efficacy was assessed using the Panic Attack and Anticipatory Anxiety Scale (PAAAS), the Agoraphobic Cognitions Questionnaire (ACQ), the Hamilton Rating Scale for Anxiety (HAMA), the Hamilton Rating Scale for Depression (HAMD), the Global Assessment of Functioning Scale (GAF), and the Clinical Global Impression of Improvement (CGI-I). Twenty-six patients completed the trial period with a dropout rate of 16.1%. At week 12, twetny one patients were responders (81.8%), and an overall improvement on all rating scales was observed in all patients both with or without agoraphobia. Fifteen patients (57.7%) achieved remission. Olanzapine was well tolerated and the most frequent adverse effects were mild-to-moderate weight gain and drowsiness. No extrapyramidal symptoms were reported.

Low-dose risperidone monotherapy was compared with paroxetine monotherapy in a parallel-group, randomized, rater-blinded study of the treatment of panic attacks (Prosser *et al* 2009). Fifty six subjects with a history of panic attacks were randomized to receive either risperidone or paroxetine. The subjects were then followed for eight weeks. Outcome measures included the Panic Disorder Severity Scale (PDSS), HAMA, HAMD, the Sheehan Panic Anxiety Scale-Patient (SPAS-P), and CGI. All subjects demonstrated a reduction in both the frequency and severity of panic attacks regardless of treatment received. Overall, both treatments were effective, and no significant treatment differences emerged in primary outcome measures. Post-hoc tests suggested a faster onset of action for risperidone.

Thirty patients with a primary diagnosis of an anxiety disorder-panic disorder (PD), social anxiety disorder (SAD), or generalized anxiety disorder (GAD)-refractory to initial pharmacotherapy with an adequate antidepressant and/or benzodiazepine trial of at least 8 weeks' duration prior to study initiation received open-label augmentation with flexibly dosed risperidone for 8 weeks (Simon *et al* 2006). Risperidone augmentation at a mean dose of 1.12 ± 0.68 mg/day (range, 0.25–3.00 mg/day) resulted in a significant reduction in anxiety symptoms across disorders as measured by the CGI-Severity of Illness scale and HAMA scores and for each disorder-specific primary outcome measure – PDSS, LSAS, and HAMA in the intent-to-treat sample. Seventy percent (21/30) of participants completed the 8-week trial. Although conclusions are limited by the open-label, relatively brief nature of this trial, our data

suggest that augmentation with low-dose risperidone may be a useful option for patients with PD, SAD, or GAD refractory to adequate initial intervention with antidepressants and/or benzodiazepines.

Generalised Anxiety Disorder (GAD)

Generalized anxiety disorder (GAD) is a chronic, highly prevalent and debilitating disorder associated with significant morbidity and disability. Traditional therapies are associated with poor levels of remission, and often result in troublesome side effects. Antipsychotic augmentation of antidepressants is indicated as the second step, when the patient turns out to be partially resistant to SSRIs, buspirone, pregabalin, or anxiolytics, and when cognitive-behavioral therapy is not possible or available (Praško & Vyskočilová 2008). If remission or at least a significant improvement is not forthcoming in reasonable time (ie 8–12 weeks), one should consider switching to other SSRIs or SNRIs or MAOIs, or SGA, or adding anticonvulsant such as pregabalin, sodium valproate or gabapentin (Sussman & Stein 2003).

First generation antipsychotics

Studies of the efficacy of most FGA in GAD are missing. A double-blind, placebo-controlled, multicenter trial investigating the effect of trifluoperazine in 4-week treatment of moderate and severe GAD in 415 outpatients showed significantly greater efficacy than placebo (Mendels *et al* 1986) According to Rickelse *et al* (1993), the FGA efficacy is somewhere between the benzodiazepine and placebo effect. Examples of FGA are thioridazine (25–50 mg twice a day), chlorprothixen (15–50 mg twice a day) and flupenthixol (1–3 mg / day) and trifluoperazin (1–2 mg twice a day), fluspirilen (1.5 mg per week) and melperon (50–150 mg daily). These drugs are less effective than benzodiazepines and antidepressants, and carry risk of motor side effects mentioned above (Wurthmann *et al* 1997). FGA would be therefore be reserved for cases of antidepressant or benzodiazepines contraindication or their ineffectiveness.

Second generation antipsychotics

There is much information about quetiapine. Three randomized double-blind placebo-controlled studies were carried out. In a 6-week trial which enrolled 38 patients quetiapine (doses of 25–300 mg per day) monotherapy was significantly more effective than placebo at 2 and 4 weeks, but not at the end of the study (Brawman-Mintzer *et al* 2006).

Katzman *et al* (2008) conducted a 12-week, open-label, flexible-dose study to assess the efficacy and tolerability of quetiapine as an adjunctive treatment to traditional medication. Forty outpatients with GAD who had not achieved remission following at least 8 weeks of an adequate dose of therapy as ussual were enrolled. The primary endpoint was the mean change from pre-treatment to week 12 in HAMA total scores.

Secondary endpoints included: the proportion of patients achieving remission (HAMA total score 10 or less at week 12), CGI-S, CGI-I, Pittsburgh Sleep Quality Index (PSQI) and Penn State Worry Questionnaire (PSWQ). Adjunctive quetiapine (mean dose 386mg/day at week 12) significantly reduced the HAMA total scores from pre-treatment (29.8 ± 9.0) to week 12 (9.0 ± 10.2) (−20.6; p<0.001). The HAMA remission rate was 72.1% at week 12. Adjunctive quetiapine resulted in a significant reduction in all efficacy measures by study end. Quetiapine was well tolerated: the most common adverse event (AE) was sedation, with no incidence of serious AEs and no clinically significant changes in vital signs, weight (mean gain 0.5kg at week 12) or laboratory assessments. The results of this small pilot trial suggest that quetiapine adjunctive to traditional therapy may be a useful treatment in patients with GAD or treatment-resistant GAD, and warrant further investigation.

In another study, 863 patients were randomized to 10 weeks of treatment with extended release quetiapine (50 or150 mg/day), paroxetine (20 mg / day) as an active comparator, or placebo (Chouinard *et al* 2008). Both doses of quetiapine and paroxetine were significantly more effective than placebo (HAMA: Hamilton Rating Scale for Anxiety Anxiety, Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire), and somatic symptoms have improved significantly in comparison with placebo at 150 mg quetiapine only. Effect of quetiapine in comparison with placebo was significantly different from placebo after 4 days of treatment. Side effects of quetiapine were minimal, occurring in less than 10% of patients. These were dry mouth, drowsiness, fatigue, headache, and dizziness. Side effects like extrapyramidal syndrome (akathisia, restlessness, tremor, motor retardation, dyskinesia, hypertonus, muscle rigidity, psychomotor hyperactivity, occurred in in 8.4% of the patients on paroxetine and in 0,9–1,8% on quetiapine). Sexual side effects occurred in 2–3% of quetiapine patients, which is significantly lower than for paroxetine. In the third study, patients were randomized to a 10-week treatment with extended release quetiapine at three different doses (50 mg or 150 mg or 300 mg per day) or placebo (Joyce *et al* 2008). Only the doses 50 and 150 mg were significantly more effective than placebo.

Forty patients who continued to experience GAD symptoms despite current anxiolytic treatment of at least 4 weeks' duration, as evidenced by HAMA total score 18 and more and CGI-S score of moderate or greater, completed a 1-week screening phase and were then randomly assigned to 5 weeks of double-blind adjunctive treatment with placebo or risperidone at flexible doses of 0.5 to 1.5 mg/day (Brawman-Mintzer *et al* 2005). Patients continued to take their anxiolytics throughout the study. Adjunctive risperidone was associated with statistically significant improvements in core anxiety symptoms, as demonstrated by greater

reductions in HAMA total scores (p = .034) and HAMA psychic anxiety factor scores (p = .047) compared with placebo. Although change scores on other outcome variables, including response rates, were higher in the risperidone group, differences did not achieve statistical significance.

Gao *et al* (2009) reviewed studies using SGAs in GAD patients and conclude, that olanzapine, risperidone and quetiapine immediate release have been explored in the treatment of refractory GAD and risperidone in bipolar anxiety with randomized, double-blind, placebo-controlled trials, but the results were not consistent. By contrast, quetiapine extended release (quetiapine-XR) 150 mg/day monotherapy yielded consistent anxiolytic effects across three studies that were superior to placebo and as effective as paroxetine 20 mg/day and escitalopram 10 mg/day but with an earlier onset of action. In a 52-week treatment of GAD, quetiapine-XR was superior to placebo in the prevention of anxiety relapses. Overall, atypical antipsychotics were relatively well tolerated, with common side effects of somnolence and sedation. However, in contrast to antidepressants and benzodiazepines, the long-term risk and benefit of atypical antipsychotics in the treatment of GAD is yet to be determined.

Bandelow *et al* (2010) made multicentre, double-blind, randomized, placebo- and active-controlled, trial consisted of a 1–4-weeks enrolment/wash-out period and a 10-week (8-week active treatment, 2-week post-treatment drug-discontinuation) study period; 873 patients were randomized to 50 mg or 150 mg quetiapine XR, 20 mg paroxetine, or placebo. Primary endpoint was change from randomization at week 8 in HAMA total score. At week 8, all active agents produced significant improvements in HAMA total and psychic subscale scores vs. placebo; HAMA somatic subscale scores were significantly reduced only by 150 mg quetiapine XR. Significant separation from placebo in HAMA total score was observed at day 4 for 50 mg quetiapine XR and 150 mg quetiapine XR, but not for paroxetine. Remission (HAMA total score 7) rates at week 8 were significantly higher for 150 mg quetiapine XR (42.6%, p<0.01) and paroxetine (38.8%, p<0.05) vs. placebo (27.2%). The most common adverse events (AEs) were dry mouth, somnolence, fatigue, dizziness, and headache, for quetiapine XR, and nausea, headache, dizziness for paroxetine. A lower proportion of patients reported sexual dysfunction with quetiapine XR [0.9% (50 mg), 1.8% (150 mg)] than with placebo (2.3%) or paroxetine (7.4%). The incidence of AEs potentially related to extrapyramidal symptoms was: quetiapine XR: 50 mg, 6.8%, 150 mg, 5.0%; placebo, 1.8%; and paroxetine, 8.4%. Author concluded that once-daily quetiapine XR is an effective and generally well-tolerated treatment for patients with GAD, with symptom improvement seen as early as day 4.

Social phobia

The treatment goals for social anxiety disorder (SAD) are to reduce fear, avoidance, physical distress, disability, and comorbidity. The selective serotonin reuptake inhibitors (SSRIs) paroxetine, sertraline, fluoxetine, fluvoxamine, and escitalopram and the serotonin-norepinephrine reuptake inhibitor venlafaxine are effective treatments. They have beneficial effects with response rates ranging from 50 to 80% in social phobia. For people who do not respond to serotonin reuptake inhibitors, treatment options include benzodiazepines (clonazepam, alprazolam, and bromazepam), alpha-2-delta calcium-channel blockers (gabapentin and pregabalin), reversible inhibitors of monoamine oxidase A (moclobemide), antiepileptics (levetiracetam), and atypical antipsychotics. Reports have suggested an effect of the atypical antipsychotic olanzapine and quetiapine in social phobia. SGA are indicated for augmentation of antidepressants treatment in patients with social phobia who appear to be resistant to SSRIs, MAOIs, anxiolytics, and when cognitive-behavioral therapy is not possible or available (Praško & Prašková 2008). This recommendation is based on clinical experience and a few published data on olanzapine, risperidone and quetiapine. Preliminary observations in 12 patients suggest an anxiolytic effect of olanzapine (Barnett *et al* 2002) confirmed the effect, however, we need more extensive study. This study was an 8-week, double-blind, placebo-controlled evaluation of olanzapine as monotherapy in which 12 patients with social phobia were randomized to either olanzapine (n = 7) or placebo (n = 5). An initial dose of 5 mg/day was titrated to a maximum of 20 mg/day. In the intent-to-treat analysis, olanzapine yielded greater improvement than placebo on the primary measures. Both treatments were well tolerated, although the olanzapine group had more drowsiness and dry mouth. Olanzapine and placebo were both associated with negligible weight gain.

Simon *et al* (2006) implemented an 8-week open trial of risperidone which was used as augmentation therapy in 30 patients with generalized anxiety disorder, social phobia or panic disorder who have not responded adequately to the maximum tolerated dose of an SSRI or a benzodiazepine after 8 weeks of treatment. Seven of the patients (23.3%) included in the study had a diagnosis of social phobia. The mean dose of risperidone was 1.1 mg per day. In the study there was a significant decrease in HAMA and CGI-S in all patients of the study. Patients with social phobia in LSAS (Liebowicz Social Anxiety Scale) scores decreased from 81.3 ± 19.7 to 38.4 ± 24.0.

Vaishnavi *et al* (2007) conducted a controlled trial of quetiapine monotherapy in SAD. 18 patients were randomized to quetiapine (up to 400 mg/day) or placebo for 8 weeks. The Brief Social Phobia Scale (BSPS) and the Clinical Global Impression of Improvement Scale (CGI-I) were the primary outcome measures, while the Social Phobia Inventory (SPIN) and the Sheehan Dis-

ability Inventory (SDI) were secondary measures. There was no significant difference on the BSPS score at endpoint between the quetiapine and placebo groups. 20% of the quetiapine patients had a 50% or greater drop in BSPS score at the end of the trial compared to baseline, while 0% had such a drop in the placebo group. There was no significant difference in responders (CGI-I score of 1 or 2) versus non-responder (CGI-I score of 3 or more) across the groups. However, 40% of quetiapine patients and 0% of the placebo patients showed much or very much improvement on the CGI-I.

The purpose of Donahue *et al* (2009) study was to provide a rigorous test of the acute impact of a single dose of quetiapine (25mg) on SAD symptoms. Individuals with SAD (N=20) were exposed to a 4-min virtual reality (VR) public speaking challenge after having received quetiapine or placebo (double-blind) 1h earlier. A parallel VR challenge occurred 1 week later using a counter-balanced cross-over (within subject) design for the medication-placebo order between the two sessions. There was no significant drug effect for quetiapine on the primary outcome measures. However, quetiapine was associated with significantly elevated heart rate and sleepiness compared with placebo. Study findings suggest that a single dose of 25mg quetiapine is not effective in alleviating SAD symptoms in individuals with fears of public speaking.

Obsessive-compulsive disorder

Treatment resistant OCD is diagnosed if there was no significant improvement in symptoms after adequate treatment of pharmaceuticals and cognitive-behavioral therapy. Adequate treatment should represent a minimum period of 10 to 12 weeks on maximum tolerated dose of an SSRI, SNRI, or clomipramine, or at least 20 to 30 hours CBT with exposure plus response prevention (Kosová *et al* 2008).

Improvements were described in 17 OCD patients resistant to fluvoxamine (with or without tic disorder) after augmentation by pimozide (McDougle *et al* 1990). A double-blind, placebo-controlled experiment was conducted by the same team using haloperidol (2 mg/day) added to fluvoxamine (McDougle *et al* 1994). After augmentation with haloperidol, patients were significantly improved in comparison with placebo Eleven of the 17 patients achieved greater than 35% improvement with haloperidol augmentation. Patients with tic disease appeared to respond better than those without it. The small size of the sample limits the ability to draw generalized conclusions Some patients experienced extrapyramidal side effects. Therefore, treatment should begin with very low doses of haloperidol (eg starting dose of 0.25 to 0.5 mg/day with a slow escalation to final dose 2–4 mg/day (McDougle & Walsh 2001).

Adding the atypical neuroleptic risperidone to a serotonin reuptake inhibitor (SRI) has benefited patients with treatment-refractory obsessive-compulsive disorder (OCD). Risperidone has been used perhaps most frequently for treatment augmentation in OCD. Four case reports of risperidone augmentation (McDougle *et al* 1995; Saxena *et al* 1996; Stein *et al* 1997; Pfanner *et al* 2000) pointed to its good efficacy. These reports were followed by a double-blind, placebo-controlled trial of augmentation with risperidone (mean 2.2 mg/day) in 36 patients who did not respond to 12 weeks of treatment with SRI (clomipramine = + SSRI). In an analysis of 33 patients who completed the experiment, risperidone was more successful than placebo (31.8% improvement on average in the Y-BOCS (Yale-Brown Obsessive Compulsive Scale). Fifty % of patients were „significantly improved" or „partially improved". There was no difference between those who had tics and those who did not. However, there were fewer responders among those who had failed on two or more SSRI, than among those who had failed only one trial with antidepressants (McDougle *et al* 2000).

A smaller double-blind study, organized by Hollander *et al* (2003) in patients who have not responded to at least two treatment attempts with SRI (clomipramine + SSRI). Four out of ten patients randomized to risperidone (0.5–3 mg/day), responded positively to treatment (CGI-I ≤ 2, a decrease in Y-BOCS ≥ 25%) within 8 weeks, while placebo has improved none of the six patients allocated to this treatment. The third study with risperidone was designed by Erzegovesi *et al* (2005). Small doses of risperidone (0.5 mg/day) were added and compared with placebo in OCD patients resistant to fluvoxamine. The study included 45 patients with OCD (39 patients completed), who participated for 12 weeks in an open study of fluvoxamine monotherapy and then were randomized to placebo or risperidone augmentation. Augmented treatment continued, double-blind, for 6 weeks. The results showed a significant effect of risperidone in patients who were refractory to fluvoxamine alone. Risperidone was well tolerated, except for mild transient sedation at the beginning, and slightly increased appetite. This preliminary study shows that even very small doses of risperidone (0.5 mg/day) are effective in OCD patients who responded poorly to a standard treatment with fluvoxamine. Adding risperidone in OCD patients refractory to SRI treatment (clomipramine + SSRI) seems to be a safe and effective treatment strategy.

Adding olanzapine to fluvoxamine (Bogetto *et al* 2000) also led to an improvement in patients insufficiently responsive to treatment with fluvoxamine. Further case reports with olanzapine (Weiss *et al* 1999) showed the good effect of antipsychotic augmentation of SRI. Koran *et al* (2000) included 10 adult patients who had previously shown resistance to 10-week treatment with fluoxetine (> or =60 mg per day) in an open observational study. The subjects had a mean baseline Y-BOCS score of 29.0 ± 4.9, suffer from OCD for more than 1 year, and had Y-BOCS score 18 or higher.

Two weeks after olanzapine, 2.5 mg/day, was added, and in the absence of responder status (Y-BOCS score decrease > or =25%) and limiting side effects, authors increased the dose to 5 mg/day, and after 2 more weeks, to 10 mg/day for 4 weeks. Nine patients completed the trial. The subjects' mean endpoint Y-BOCS score was 24.4 ± 8.0 (a 16% decrease). The 3 responders' Y-BOCS scores dropped 68%, 30%, and 29%, but only 1 patient was rated „much improved." He maintained this improvement during a 6-month follow-up period taking olanzapine, 5 mg/day. Improvement in OCD was independent of improvement in mood symptoms. Six patients (60%) experienced significant weight gain.

The efficacy of olanzapine augmentation of SSRI treatment has been corroborated in two case series (Francobandiera 2001; Crocq *et al* 2002). Francobandiera evaluetes the clinical response to olanzapine used in association with SSRIs or clomipramine in treatment-resistant OCD. He describes the cases of 9 patients with SSRI-resistant OCD who were given an open-label adjunctive treatment of olanzapine for a minimum Of 6 weeks. Six patients showed improvement of symptoms after the augmentation with olanzapine. One patient (treated with clomipramine) discontinued olanzapine due to side effects, and another 2 did not respond.

Twenty-one patients unresponsive to treatment with paroxetine, administered for at least 12 weeks at the dose of 60 mg/day, participated to a 12-week open-label, add-on trial with olanzapine (10 mg/day) (D'Amico *et al* 2003). The psychopathological state was evaluated by the Y-BOCS and CGI. Three patients did not complete the 12-week adjunctive treatment with olanzapine. In the 18 completers, the mean Y-BOCS score decreased significantly from 27.1 ± 4.0 at baseline to 20.1 ± 3.9 at final evaluation (p<.001). After 12 weeks, 38.9% of patients improved. This study also showed that the addition of olanzapine did not change plasma levels of paroxetine. The combination was well tolerated.

In a double-blind, placebo-controlled study of 44 partial responders or non-responders at 8 weeks with fluoxetine (Shapiro *et al* 2004), olanzapine (5–10 mg/day) augmentation was not effective. Nine of 22 (41%) patients showed at least a 25% decrease in Y-BOCS scores for both olanzapine and in the placebo group. The problem with this study is a short (8-week) treatment with fluoxetine before the start of augmentation, and the inclusion of partial responders to fluoxetine.

However, Bystritsky *et al* (2004) selected a more treatment resistant group of 26 OCD patients who have not responded to at least 12 weeks of SRI treatment and a trial of behavioral therapy. Eleven of the 13 patients treated with olanzapine (average dose 11.2 mg/day) and seven of the 13 on placebo completed the study. After 6 weeks of treatment, olanzapine was significantly more effective than placebo. The average decrease in Y-BOCS was 16%, but after augmentation with placebo were no improvements. Six (46%) of the olanzapine group met the response criteria (25% decrease in Y-BOCS). However, the high dropout rate among patients on placebo precluded meaningful statistical analysis . The above results show that olanzapine augmentation requires further verification.

Augmentation of SRI by quetiapine showed variable findings. Open studies suggested a good effect in more than 50% of treated patients (Denys *et al* 2002; Sevincok & Topuz 2003; Bogan *et al* 2005), although other studies showed little effect (Mohr *et al* 2002). Larger open study with 27 patients with resistant OCD has found a clinical response in 14 of them (64%) (Atmaca *et al* 2002). Three recent double-blind, placebo-controlled study of quetiapine showed contradictory results. Fineberg *et al* (2005) studied 21 OCD patients without significant comorbidities who have not responded adequately to a 6-month treatment with SRI. The SRI treatment was augmented by quetiapine (≤ 400 mg/day) or placebo. One patient dropped out from each group and quetiapine was well tolerated. In the group with quetiapine augmentation, the symptoms were reduced on average by 14%, and in the placebo group by 6%. Response to quetiapine was variable, with most patients showing effects similar to those seen in the placebo group.

Forty-two patients who responded inadequately after 12 weeks of SRI were randomized to 6 weeks of augmented treatment with placebo or flexible doses of quetiapine (Carey *et al* 2005). In both groups there was a significant improvement and 40% of patients on quetiapine and 47.6% on placebo were classified as responders. There was no significant difference between groups. In contrast, another double-blind, placebo-controlled study with 40 patients (Denys *et al* 2004) showed a significant effect of quetiapine augmentation in patients who previously failed to respond to at least two courses of SRI treatment. After 8 weeks of augmentation, the 20 patients on quetiapine showed significantly greater reduction in scores on the Y-BOCS than placebo augmentation (31% vs. 6%). In another study, 40% of patients on quetiapine but only 10% on placebo showed clinical improvement (Pallanti *et al* 2002). Denys *et al* (2007) in a double-blind, placebo-controlled study examined whether the type and dose of SRI influences the outcome of quetiapine augmentation. Treatment effect was evaluated in 102 patients. Clomipramine, fluoxetine and fluvoxamine augmentations were more effective than adding placebo. Lower doses of antidepressants were associated with more effective augmentation.

The objective of the Kordon *et al* (2008) study was to evaluate the efficacy of quetiapine added to baseline treatment with SRIs for the treatment of OCD in severely ill adult subjects. Forty patients (21 men, 19 women) with primary OCD participated in a 12-week, double-blind, placebo-controlled trial. They were randomly assigned to dosages of quetiapine titrated up to 400 mg/d (n = 20) or to placebo (n = 20) in addition to their SRI treatment. During the continuation phase (weeks 6–12), subjects received different dos-

ages between 400 and 600 mg/d depending on clinical response. At entry, all patients were unresponsive to at least 1 course of at least 12 weeks of treatment with SRIs at defined doses. The total Y-BOCS score was the primary efficacy parameter. Intention-to-treat, last-observation-carried-forward analysis demonstrated a mean decrease in Y-BOCS score of 5.2 ± 5.4 in the quetiapine group and 3.9 ± 4.9 in the placebo group. The analysis of treatment effects between the 2 groups showed no significant difference. There were no significant group differences in any of the other self-rating scales or clinician-administered rating scales. Authors concluded that in this study, augmentation of SRI treatment with quetiapine in severe OCD had no additional effect.

The study of Vulink *et al* (2009) was done to assess the efficacy of quetiapine addition to citalopram in treatment-naive or medication-free obsessive-compulsive disorder (OCD) patients. Seventy six drug free or drug naive patients were randomly assigned in a 10-week, double-blind trial with citalopram (60 mg/day) plus quetiapine (300–450 mg/day) or placebo. Treatment-refractory OCD patients were excluded. 66 patients completed the trial; 31 in the quetiapine and 35 in the placebo group. Response was defined as a 35% or greater reduction on the Y-BOCS and a CGI-I score at endpoint of 1 or 2. As measured by the mean reduction in Y-BOCS scores following an intent-to-treat, last-observation-carried-forward analysis, quetiapine addition (11.9) was significantly superior to placebo (7.8; p = .009). Quetiapine addition was also significantly superior to placebo on the CGI-I scale, with a mean CGI-I score of 2.1 ± 1.3 versus 1.4 ± 1.2, respectively (p = .023). Quetiapine addition (N = 22, 69%) was also associated with a significantly greater number of patients responding to treatment compared with placebo addition (N = 15, 41%; p = .019). More patients receiving quetiapine (N = 8) than placebo (N = 2; NS) discontinued treatment due to adverse events. Authors conclude that the combination of quetiapine and citalopram was more effective than citalopram alone in reducing OCD symptoms in treatment-naive or medication-free OCD patients.

One positive open-label study used amisulpride augmentation (200–600mg/day) added to the SRI-resistant OCD in 20 patients (Metin *et al* 2003). Clozapine monotherapy in 12 patients with treatment resistant OCD showed no effect (McDougle *et al* 1995). Aripiprazol (10–30mg/day) was also studied as monotherapy in an open study of the combined group of patients with drug-resistance and in drug-naive patients (Connor *et al* 2005). Two of the patients dropped out because of side effects and the group as a whole showed no significant change, although two patients were classified as responders.

Sareen *et al* (2004) made MEDLINE and PsychInfo search (1980–2003) to collect published reports of the interactions between antipsychotics and OCD symptoms. In the placebo-controlled trials with haloperidol, risperidone, olanzapine, and quetiapine, a significantly higher response rate (46–71%) was found for the antipsychotic groups, compared to no response for the placebo groups. Reports of exacerbation of OCD symptoms with the use of atypical antipsychotics were limited to individuals with a primary psychotic disorder.

Keunerman *et al* (2005) made literature search to review the role of antipsychotic medications in the treatment of OCD from year 1966 to 2003. According the authors the earlier studies of augmentation of serotonergic antidepressants (SRIs) with typical antipsychotics including haloperidol and pimozide in OCD demonstrated favourable responses, also highlighting patient subgroups with robust treatment response. Studies examining augmentation with atypical agents are emerging. SRI-resistant OCD patients are likely to benefit from augmentation with atypical antipsychotics in around 50% of cases. While there is little role for antipsychotic monotherapy in OCD, there is growing evidence in support of adjunctive antipsychotics in OCD refractory to serotonin-reuptake inhibitors (SRIs). Particular subgroups of OCD patients, notably those with comorbid tic disorder and those with schizotypal personality disorder, have been shown to respond more robustly to augmentation strategies in some trials of both typical and atypical antipsychotics.

Bloch *et al* (2006) conducted a meta-analysis of the augmentation with antipsychotics in OCD patients resistant to serotonergic antidepressants. Search results and analysis were limited to double-blind, randomized control trials involving the adult population. The analysis included 278 patients from 9-studies. The response criterion used was a 35% reduction of Y-BOCS score. The subgroup of OCD patients with comorbid tics have a particularly beneficial response to this intervention. Antipsychotic augmentation in SRI-refractory OCD is indicated in patients who have been treated for at least 3 months of maximal-tolerated therapy of an SRI. Unfortunately, only one-third of treatment-refractory OCD patients show a meaningful treatment response to antipsychotic augmentation. There is sufficient evidence in the published literature, demonstrating the efficacy of haloperidol and risperidone, and evidence regarding the efficacy of quetiapine and olanzapine is inconclusive. Patients with comorbid tics are likely to have a differential benefit to antipsychotic augmentation.

Maina *et al* (2008) presented the study with aim to investigate in a single-blind manner, over a period of 8 weeks, the comparative efficacy and tolerability of risperidone versus olanzapine addition in the treatment of OCD patients who did not show 35% or more decrease in the Y-BOCS score after 16-week SRI treatment (defined as resistant). The study consisted of two different phases: a 16-week open-label prospective phase to ascertain resistance to SRI treatment and an 8-week single-blind addition phase for resistant subjects only. Ninety-six subjects with OCD entered the open-label prospective phase; at the end of the 16-week period, 50

(52%) were judged to be resistant and were randomized to receive risperidone (1 to 3 mg/d) or olanzapine (2.5 to 10 mg/d) addition for 8 weeks. Overall, patients in both groups responded significantly, without differences between the two treatment groups; although no differences emerged for the proportion of patients reporting at least an adverse event, the profiles of adverse experiences differed significantly, being risperidone associated with amenorrhoea and olanzapine with weight gain.

Although atypical antipsychotic agents have been found effective in the augmentation of serotonin reuptake inhibitors (SRIs) for treatment-resistant obsessive-compulsive disorder (OCD) in short-term trials, there are few data on the effectiveness and safety of these agents in clinical settings over the long term. Matsunaga *et al* (2009) made a long-term trial of effectivenes of atypical antipsychotics in augmenting SSRI-refractory OCD. Subjects (N = 46) who responded to selective SRIs (SSRIs) in an initial 12-week trial were continued on SSRI monotherapy plus cognitive-behavioral therapy (CBT) for 1 year. Subjects (N = 44) who failed to respond to SSRIs were randomly assigned to 1 of 3 atypical antipsychotics – olanzapine, quetiapine, or risperidone – and were consecutively treated using SSRI + atypical antipsychotics combined with CBT for 1 year. Augmentation with atypical antipsychotics reduced mean Y-BOCS) total scores in SSRI-refractory OCD patients (from 29.3 ± 9.9 at initial assessment to 19.3 ± 6.8 after 1 year). However, compared to SSRI responders (decreased from Y-BOCS 25.8 ± 11.4 at initial assessment to 13.7 ± 4.6 after 1 year), total Y-BOCS scores in those who required atypical antipsychotic augmentation were initially higher, and they remained at higher levels than those of SRI responders after 1 year of the treatments. This work does not sufficiently support the long-term effectiveness of the atypical antipsychotics in the augmentation of SSRIs for treatment-resistant OCD patients.

According ECNP Consensus Meeting, March 2008 (Goodwin *et al* 2009), SSRI monotherapy has moderate overall average benefit in OCD and can take as long as 3 months for benefit to be decided. Antipsychotic addition may be considered in OCD with tic disorder and in refractory OCD. For OCD with poor insight (OCD with „psychotic features"), treatment of choice should be medium to high dose of SSRI, and only in refractory cases, augmentation with antipsychotics might be considered. Augmentation with haloperidol and risperidone was found to be effective (symptom reduction of more than 35%) for patients with tics. For refractory OCD, there is data suggesting a specific role for haloperidol and risperidone as well, and some data with regard to potential therapeutic benefit with olanzapine and quetiapine.

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) is a prevalent and disabling mental illness. The selective serotonin reuptake inhibitors are considered the first-line pharmacological treatment for PTSD. However, even when treated with this class of drugs, response rates rarely exceed 60% and less than 20–30% of the patients achieve full remission (Berger *et al* 2009). A reduction of symptoms by 30% at 8 weeks and 50% at 12 weeks is not considered adequate response to treatment. It is then appropriate to consider a switch to another SSRI or tricyclic antidepressants (TCA) or mood stabilizer. In partial response (approximately 30% of symptom reduction), treatment augmentation be selected according to the predominant symptoms of the patient (Praško 2008). Next list show exaples and treatment recommendations:

- add evening TCA or nefazodone for sleep disorders
- mood stabilizers for hyperarousal or impulsivity
- buspirone or short-term benzodiazepines for significant somatic symptoms
- antipsychotics for intrusive thoughts flashbacks or psychotic symptoms antipsychotic.

Psychotic symptoms that frequently occur in combat-related posttraumatic stress disorder (PTSD) complicate its pharmacotherapy. Psychotic features, such as hallucinations, delusional interpretation of reality or oneiroid states may occur as intrusive reexperiencing of past events or be the result of comorbid disorders such as depressive illness or drug abuse (Hamner 1997). Antipsychotics should always be used in such cases. In a published case report, clozapine was successful in a Vietnam veteran suffering from PTSD with comorbid paranoia, hallucinations and thought disorder (Hamner 1996).

Pilot studies published by Hamner al. (2001) used quetiapine as adjunctive treatment for war veterans with or without psychotic symptoms. There was a significant improvement in PTSD, in both positive and negative symptoms in the PANSS, and in depressive symptoms after 5 weeks

DeFaria *et al* (2001) added risperidone at flexible doses to antidepressants, mood stabilizers, or anxiolytics in the treatment of veterans with PTSD with or without psychotic features. After 12 weeks, they found a significant effect both on the core symptoms of PTSD and the associated psychotic symptoms. In another study, Kaye *et al* (1987) used risperidone as adjunctive treatment to antidepressant medication under double blind conditions versus placebo in 40 patients with chronic PTSD with or without psychotic features. Active medication resulted,in a significant reduction of both positive and negative symptoms of the PANSS and intrusive reexperiencing of past events in CAPS (Cli-

nician-Administered PTSD Scale) in a 5-week study (Hamner *et al* 2000, 2003).

Butterfield *et al* (2001) compared olanzapine at doses of 5–20 mg / day with placebo in patients with chronic PTSD in a controlled trial. Olanzapine was significantly more effective than placebo. Similarly, Stein *et al* (2002) add olanzapine or placebo in a double-blind study of 19 war veterans who had minimallyimproved after 12 weeks of SSRI. After olanzapine, in contrast to placebo, patients experienced a significant reduction of PTSD symptoms.

Patients with PTSD showing psychotic features who failed to respond to antidepressant treatment were given monotherapy trials with fluphenazine (n = 27), olanzapine (n = 28), risperidone (n = 26), or quetiapine (n = 53) in an open-label retrospective study (Pivac & Kozaric-Kovacic 2006). Inpatients with combat-related PTSD were treated for 6 weeks with fluphenazine (n=27), olanzapine (n=28), risperidone (n=26), or quetiapine (n=53) as a monotherapy. Treatment response was assessed by the reduction in total and subscales scores in the clinical scales measuring PTSD (PTSD interview and Clinician-administered PTSD Scale) and psychotic symptoms (Positive and Negative Syndrome Scale. After 6 weeks of treatment, monotherapy with fluphenazine, olanzapine, risperidone, or quetiapine in patients with PTSD significantly decreased the scores listed in trauma reexperiencing, avoidance, and hyperarousal subscales in the clinical scales measuring PTSD, and total and subscales scores listed in positive, negative, general psychopathology, and supplementary items of the Positive and Negative Syndrome Scale subscales, respectively (P<0.001). PTSD and psychotic symptoms were significantly reduced after monotherapy with typical or atypical antipsychotics. All the treatments were effective, with olanzapine and risperidone showing better efficacy on some measures. As psychotic symptoms commonly occur in combat-related PTSD, the use of antipsychotic medication seems to offer another approach to treat a psychotic subtype of combat-related PTSD resistant to previous antidepressant treatment.

Villarreal *et al* (2007) assessed the efficacy and safety of aripiprazole in outpatients with PTSD on a 12-week, open-label trial. Twenty-two subjects participated; 16 were combat veterans. The primary outcome measure was CAPS. Secondary outcome measures included the Positive and Negative Symptoms Scale and the Hamilton Depression and Anxiety Scales. All subjects had a CAPS score 60 or more at baseline. Lifetime history of psychotic disorders or bipolar illness was exclusionary. Fourteen subjects completed 12 weeks of treatment. Eight subjects dropped-out due to side effects. For patients who discontinued, missing values were estimated using „the last observation carried forward" method. Significant improvements were seen on: CAPS total, all its subscales, positive symptoms, anxiety and depression scores. Fourteen participants were classified as responders, defined by 20% or greater improvement

on CAPS total score. Of the 13 subjects who completed final ratings, CAPS total scores improved significantly (P = .011). The mean daily dose of aripiprazole was 12.95 mg. The most common side effects were somnolence (54.5%), restlessness (50%), insomnia (36.4%), and asthenia (31.8%). The initially high dropout rate may be related to intolerability due to a high starting dose (10 mg), suggesting beginning treatment at lower doses.

Pae *et al* (2008) published the results of a meta-analysis of existing randomized, double-blind, placebo-controlled clinical trials (RCTs) SGAs as a monotherapy or augmentation therapy for the treatment of patients with PTSD. Seven RCTs were identified through extensive scans of databases. Dichotomous and continuous measures were performed using a fixed effects model, heterogeneity was assessed, and subgroup analyses were done. Data from seven RCTs involving a total of 192 PTSD patients (102 randomized to SGAs and 90 randomized to placebo) were analyzed. The results show that SGAs may have a beneficial effect in the treatment of PTSD, as indicated by the changes from baseline in CAPS total scores. In addition, the overall standardized mean difference of the mean changes in the three CAPS subscores was statistically significant (P=0.007) between SGAs and placebo groups, favoring SGAs over placebo. In particular, the symptom of ‚intrusion' was mainly responsible for this significance.

An exhaustive review of treatments for PTSD beyond antidepressants was published by Berger *et al* (2009). Sixty-three articles were selected, covering the following categories: antipsychotics, anticonvulsants, adrenergic-inhibiting agents, opioid antagonists, benzodiazepines and other agents. None of the identified agents reached the level A of scientific evidence, 5 reached level B, 7 level C and 13 level D. The nonantidepressant agent with the strongest scientific evidence supporting its use in PTSD is risperidone, which can be envisaged as an effective add-on therapy when patients did not fully benefit from previous treatment with SSRIs.

Discussion

Off-label use antipsychotics, particularly SGA, in anxiety disorders and OCD appears to be common. SGA is typically used in patients who fail to respond to an antidepressant. Most of the evidence supporting this practice is concerned with SGA added to an antidepressant as augmentation treatment.

The evidence is of varying quality. There is a limited number of randomized placebo-controlled, doubleblind trials of SGA augmentation. The typical design enrolled patients whose resistence to antidepressant treatment hed been determined prospectively or retrospectively. The principal contrast was between the two augmentation treatments (SGA v placebo). The effect size was generally not considered in the design of these

studies, power analysis was not conducted, and the numer of subjects was usually small so that the studies may have been underpowered. These and similar design problems may have contributed to the „negative" findings is some studies In general, the randomized controlled studies yielded some support for SGA supplementation, the evidence seems to be moderately strong for risperidone in OCD.

Most of evidence supporting SGA augmentation treatment is based on prospective or retrospective open studies and case reports. As usual, these uncontrolled studies and observations show results that more supportive of the efficacy of this treatment than the controlled trials.

Conclusion

There is modest or moderate empirical evidence for the use of SGA augmentation treatment for patiens with anxiety disorder and OCD who failed to respond to antidepressants. The strength of the evidence varies across the individual SGA. The facts to date does not warrant the use of SGAs as first-line monotherapy or as first – adjunctive therapy in the treatment of anxiety disorders. Rigorous, independently funded, long-term studies are needed to support the off-label use of SGAs in the treatment of anxiety disorders. Nevertheless, some patients with refractory anxiety disorders may benefit from the judicious and carefully monitored use of adjunctive SGA. A careful risk-benefit assessment, on a case-by-case basis, must be undertaken by the physician,.

The therapeutic benefits of the SGA in such patiens need to be carefully evaluated in relation to their metabolic risks in each individual case and each individual SGA Prior to SGA augmentation, certain other steps should be taken. These include a trial of another antidepressants, adding a benzodiazepine, and checking patients adherence to the currently precribed antidepressant treatment. Futhermore, strenuous efforts should be made to provide cognitive-behavioral therapy ot other non-pharmacological treatments that might provide the patient adequate relief, obviating the need for SGA augmentaiton. The augmentaiton should not be started before exhausting these options. Once started, the clinical effects of the SGA should be monitored, and the treatment should be discountinued i fit is not found to be effective.

Finally, SGA augmentation shold only be provided with the informed consent of the patient. Baseline weight, laboratory tests including fasting glucose, insulin, and lipid panel as well as clinical examination for extrapyramidal symptoms and tardive dyskinesia should be done prior to the start of SGA treatment. These measures should be monitored periodically during the SGA treatment.

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