Expert Opinion on Investigational Drugs

ISSN: 1354-3784 (Print) 1744-7658 (Online) Journal homepage: https://www.tandfonline.com/loi/ieid20

Atypical antipsychotics as a possible treatment option for irritable bowel syndrome

Chi-Un Pae, Soo-Jung Lee, Changsu Han, Ashwin A Patkar & Prakash S Masand

To cite this article: Chi-Un Pae, Soo-Jung Lee, Changsu Han, Ashwin A Patkar & Prakash S Masand (2013) Atypical antipsychotics as a possible treatment option for irritable bowel syndrome, Expert Opinion on Investigational Drugs, 22:5, 565-572, DOI: 10.1517/13543784.2013.782392

To link to this article: https://doi.org/10.1517/13543784.2013.782392

Published online: 19 Mar 2013.

EXPERT OPINION

1. Brief overview of irritable bowel syndrome: focusing on psychiatric relevance
2. Literature search
3. Rationale for the use of AAs for the treatment of IBS
4. Clinical evidence
5. Expert opinion

Atypical antipsychotics as a possible treatment option for irritable bowel syndrome

Chi-Un Pae[†], Soo-Jung Lee, Changsu Han, Ashwin A Patkar & Prakash S Masand

[†]*The Catholic University of Korea College of Medicine, Bucheon St. Mary's Hospital, Department of Psychiatry, Bucheon, Republic of Korea*

Introduction: Irritable bowel syndrome (IBS) is a prevalent functional gastrointestinal disorder (FGID) that is characterised by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits. Although the pathophysiology of IBS is not fully understood, it is believed that psychiatric comorbidities are highly common in such patients. A variety of psychotropic medications are widely used in the treatment of IBS, particularly older antidepressants such as tricyclic antidepressants (TCAs).

Areas covered: With the advent of newer antidepressant classes with better safety and tolerability compared with TCAs, such as serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), clinicians now have more advanced treatment options for treating IBS. Additionally, some atypical antipsychotics (AAs) have recently received approval for treatment of major depressive disorder (MDD). Some AAs may have potentials based on their pharmacodynamic profile and proven benefit for mood symptoms, pain, anxiety and sleep disturbances. This article describes the potential rationale, clinical data and practical aspects involved in the use of AAs for patients with IBS.

Expert opinion: Atypical antipsychotics (AAs) may have a role in the treatment of irritable bowel syndrome (IBS) based on the currently available findings, although there is no clear evidence, and a number of clinical issues to be addressed in the use of AAs for the treatment of IBS.

Keywords: anxiety, atypical antipsychotic, depression, irritable bowel syndrome, neurotransmitter

Expert Opin. Investig. Drugs (2013) ***22****(5):565-572*

1. Brief overview of irritable bowel syndrome: focusing on psychiatric relevance

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders (FGIDs) [1]. The prevalence rate of IBS in the United States is 10 – 15%. In Asia, the prevalence is slightly less: 4.4% in Taiwan [2] and 8 – 9% in Korea [3]. In general, 7 – 10% of people worldwide are affected; however, only 10 – 30% of affected individuals seek medical attention [4,5].

The pathophysiology of IBS has not yet been clearly elucidated, but it has been suggested that IBS may exert functional gastrointestinal (GI) disturbances along with abnormal intestinal motility, incongruous intestinal gas production, enhanced intestinal nociception, and brain–gut-axis aberration [6]. It has also been suggested that IBS and psychiatric conditions have a bidirectional relationship [6]. For instance, IBS may be associated with higher rates of fibromyalgia, pain symptoms, generalised anxiety disorder (GAD), panic disorder, obsessive–compulsive disorder (OCD), dysthymic disorder, major depressive disorder (MDD) and schizophrenia;

10.1517/13543784.2013.782392 © 2013 Informa UK, Ltd. ISSN 1354-3784, e-ISSN 1744-7658

Article highlights.

- Despite the pathophysiology of irritable bowel syndrome (IBS) is not fully understood, it is believed that depression and IBS share some common pathological finding as well as IBS is also commonly comorbid with various psychiatric disorders.
- Antidepressants including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been traditionally considered as second treatment option after commencement of standard treatment of IBS.
- Atypical antipsychotics (AAs) have demonstrated their antidepressant effect through a number of animal studies and clinical trials, among which quetiapine XR and aripiprazole have been approved as an augmentation agent for treatment of major depressive disorder (olanzapine alone is not approved but a combination with fluoxetine is also approved for treatment-resistant depression).
- Preclinical studies and pilot clinical trials have supported a putative role of AAs in the treatment of IBS. The conjecture of action mechanism of AAs may include a wide range of pharmacological effects (i.e., immune alteration, neurotransmitter regulation, modulation of neurotrophic factors, mood and anxiety control, restoration of sleep architecture, hormonal balance, gut motility and analgesia).
- The management of IBS may require a multimodal treatment approach, including dietary and lifestyle modifications and effective pharmacological treatment for symptomatic control. AAs have not been approved for IBS yet. Hence, the most prudent use of AAs for IBS patients should be confined as one of supplementary treatment options after failure of guideline-based treatment options or target for difficult-to-treat IBS patients.

This box summarizes key points contained in the article.

moreover, may patients with these various disorders suffer IBS [6,7]. Hence, the management of IBS may require a multidisciplinary approach as well as effective therapeutic medications for symptomatic control [8]. In fact, tricyclic antidepressants (TCAs) are frequently used to control psychiatric comorbidities or corresponding symptoms in IBS, especially for more severe and refractory symptoms. However, most clinical data focused on TCAs were derived from clinical trials that had some methodological limitations (small sample size and trial number, etc.) [9]. Since the advent of selective serotonin reuptake inhibitors (SSRIs) with their better safety and tolerability profiles compared with TCAs, some studies have shown that SSRIs may also be effective and beneficial for patients with IBS in clinical practice [9,10]. Theoretically, based on their differential effects on intestinal transit time, SSRIs should have the most benefit in persons having IBS with constipation, and antidepressants should have the most benefit in patients having IBS with diarrhea; however, data are lacking [11].

Overall, the clinical utility of these antidepressants for the treatment of patients with IBS remains unsatisfactory to both clinicians and patients based on currently available clinical data. In this regard, recent evidence has suggested that atypical antipsychotics (AAs) may be another viable treatment option for patients with IBS. Most AAs have been primarily approved for the treatment of schizophrenia, and some also have indications for bipolar disorder and schizoaffective disorder. In fact, some AAs, such as quetiapine, aripiprazole and the combination of fluoxetine plus olanzapine, have been approved for treatment of MDD and are now the only officially approved medications as augmentation agents for MDD [12,13]. These additional treatment options represent another opportunity for patients with IBS, as IBS with comorbid medical or psychiatric conditions may be more difficult to treat, and these patients usually need more advanced treatment options rather than traditional therapy alone [11]. According to a recent study [14], approximately 80% of patients with IBS had at least one other FGID or at least one somatic comorbidity, and those with severe IBS had a higher prevalence of psychiatric (95.1%) and somatic (96.7%) comorbidities compared with patients with mild IBS. Such patients were also found to show low work productivity, increased healthcare utilisation, higher medical costs and poor clinical responses to current treatment.

2. Literature search

The Medical Subject Headings (MeSH) search is arranged hierarchically from very broad terms to very narrow terms and thereby it retrieves efficiently and only papers relating to specific themes, resulting in fewer results than expected. However, for this review, manual text word searching was adopted since the present topic should not be fully and properly covered by hierarchical search. In addition, we also considered possible omission of the most recent research by inherent weakness of MeSH search and difficulty in collection of detailed informative data due to its complexity of the present topic.

A search of the studies used the key text words 'atypical antipsychotic (individual antipsychotic name for clinical data as well), irritable bowel syndrome, functional gastrointestinal disorder, dyspepsia, comorbid, and psychiatry' from the databases, PubMed and MedLine. The studies searched were verified for publication in peer-reviewed journals. We also used reference lists from identified articles and reviews to find additional studies. No date or language constraints were utilised. Proceedings of the scientific meetings were also searched for paper and poster presentations. Data search and verification were handled first by one of the authors (C.U. P.) and then independently reassessed by (C.H). The style of this paper is brief narrative review of the potential role and clinical implications of AAs for the treatment of IBS, by which all relevant studies meeting a scope of the present review purpose were selected based on the consensus among the authors.

3. Rationale for the use of AAs for the treatment of IBS

A better understanding of the potential mechanism of AAs for IBS treatment may enhance clinicians' attention to the putative role of AAs in the treatment of IBS. For instance, norquetiapine, which is the major metabolite of quetiapine, has a high affinity for the norepinephrine transporter. This partly explains the antidepressant effects of quetiapine because these effects result in an increase in noradrenaline in the synaptic cleft, which is a crucial neurotransmission process in the development and management of MDD [15]. Ziprasidone also inhibits serotonin and norepinephrine-transporter reuptake [16]. These reuptake inhibition effects of AAs are in line with the potential mechanism of action of antidepressants in the treatment of IBS. Their analgesic mechanism of action is complex and not fully understood, but evidence suggests that their main mechanism is the inhibition of norepinephrine and serotonin reuptake in the synaptic space at both the spinal and supraspinal levels, which allows for increased activity of the neurotransmitters in the synaptic cleft [17]. Additionally, increasing evidence suggests that serotonin transporter gene polymorphisms tend to be associated with better treatment responses to serotonin 3 receptor antagonist, as well as a greater response in those with long homozygous than in those with heterozygous polymorphisms [18].

The analgesic effects of various AAs in animal acute-pain models have been described, mediated through different pathways including the opioid system [19,20]. In such preclinical studies, clozapine demonstrated a potent dose-dependent antinociceptive effect, which was reversed by an opioid antagonist. This result indicates that opioid receptors (i.e., μ1-, μ2-, κ1- and κ3-receptor subtypes) may underlie the mechanism of clozapine-induced antinociception [20]. Additionally, α2-adrenoreceptors were found to be moderately involved in clozapine-induced antinociception [20]. Compared with clozapine, the antinociceptive effect of olanzapine was more (albeit weakly) dependent on α2-adrenoreceptors (completely blocked by yohimbine) than on opioid receptors, as evidenced by weak antagonistic effects of naloxone and nonselective serotonin receptor antagonists [20]. Amisulpride, which antagonises both dopamine D2/D3 receptor subtypes, demonstrated a dose-dependent antinociceptive effect mediated by different opioid receptors (mainly μ1-, μ2- and κ1-opioid receptor subtypes) via the D2 receptor [19]. However, this antinociceptive effect was antagonised by various opioid antagonists [19]. Case reports, small-scale open-label studies and controlled clinical trials have demonstrated the analgesic effects of AAs (mostly with tiapride, olanzapine, quetiapine, risperidone and sulpiride) in patients with headache, migraine, fibromyalgia, cancer and neuralgia, although larger well-controlled clinical trials are mandatory to draw definite conclusions [21,22]. In particular, tiapride has been the most-studied AA in controlled clinical trials for FGID, but it is mostly available in Europe.

Although serotonergic-noradrenergic interactions play a major role in pain, the muscarinic cholinergic receptor antagonism of TCAs has also been suggested as a mechanism underlying the intestinal secretion inhibition that is common in IBS. This point is also in line with the action mechanism of clozapine, quetiapine and olanzapine. Most antipsychotics could have some prokinetic effect via D2 receptor antagonism in relation to their anticholinergic effect [23]. Additionally, AAs that have a profile comprising histamine (H1) antagonistic and serotonin 1A agonistic effects, such as quetiapine, may reduce intestinal contraction and abdominal pain. Sulpiride has also been found to affect intestinal transit time, resulting in alteration of bowel motility [24].

Abnormal hypofunction in hippocampal glutamatergic neurotransmission in patients with IBS without psychiatric comorbidity, possibly as a result of chronic pain, was proposed in a preliminary report [25]. The effect of quetiapine on glutamate receptor activity leading to the restoration of normal glutamatergic neurotransmission should be notable in consideration of glutamate alteration in IBS [26].

IBS is also characterised by an increase in proinflammatory cytokines [27], which may also be affected by AAs [28]. In particular, olanzapine and quetiapine may affect the immune system directly or possibly through anti-histaminergic mechanisms, resulting in the commencement of a cascade of events leading to a reduction in proinflammatory cytokine levels (i.e., TNF-α and IL-6) [29].

Alteration of neurotrophins such as brain-derived neurotrophic factor and nerve growth factor in IBS and its correlation with abdominal pain have also been proposed [30]. AAs are known to increase levels of brain-derived neurotrophic factor, improve cell survival and enhance neurogenesis, whereas typical antipsychotics do not have these effects [31].

Interestingly, over the years, strong associations between GI pathologies and psychiatric disorders have been reported. However, it has been difficult to distinguish cause from effect and to characterise how antipsychotics impact GI symptoms [32]. The prevalence of IBS in psychiatric diseases is known to be higher than that in the healthy population [33]. AAs are involved in alteration of GI motility and have been found to reverse alterations in some intestinal inflammatory markers responsible for the development of IBS, such as anti-*Saccharomyces cerevisiae* antibody (ASCA) in patients with schizophrenia [32].

Compared with placebo, short-term nonabsorbable antibiotics are more effective for the treatment of bloating and global improvement of IBS [11]. According to an anecdotal study [34], antipsychotics were able to reduce or reverse the resistance of Gram-positive and Gram-negative bacterial strains to antibiotics to which these strains were initially resistant.

Finally, over-activation of the hypothalamic–pituitary–adrenal axis (HPA axis) has also been involved in the development of IBS [27], and some AAs have an effect on the attenuation of the HPA axis [35]. Of these, olanzapine and quetiapine are particularly associated with a decrease in plasma

adrenocorticotropic hormone and cortisol concentrations [36]. **Table 1** summarises the potential mechanism of action of AAs for IBS.

4. Clinical evidence

To date, there have been no double-blind, placebo-controlled, adequately powered clinical trials of AAs for the treatment of IBS. A handful of pilot clinical trial data suggest the potential role of AAs for the treatment of IBS; however, such studies are all case reports or small-scale, open-label studies [17]. In a recent retrospective study, low doses of quetiapine (25 – 100 mg) were used for patients with severe IBS who showed inadequate antidepressant responses, developed intolerable adverse events (AEs), had comorbid anxiety disorders, suffered sleep disturbances or sustained pain symptoms despite maximal antidepressant doses [37]. Twenty one patients were identified and interviewed. In that study, the initial quetiapine doses ranged from 25 – 100 mg (25 mg for 8 patients, 50 mg for 7 patients, and 100 mg for 6 patients). The dose was flexibly adjusted based on clinical need or AEs, and the mean dose of quetiapine was 50 mg. Eleven of the 21 patients (52.3%) were undergoing quetiapine treatment at the time of the interview. The mean duration of treatment at the time of the interview was 145 days (range, 28 – 450 days). Of these 11 patients, approximately 55% reported adequate relief of symptoms. In terms of the primary outcome measure for clinical response, 9 patients (82%) were satisfied with the results of their treatment; they were engaging in more activities and coping better, and they reported improved symptoms. Four found the treatment to be more helpful than expected. This trend toward supporting the effects of quetiapine in the treatment of IBS was also observed in secondary endpoints, compared with before initiation of treatment, in 36.4% of patients. More than 50% of patients with severe refractory IBS who continued quetiapine augmented with antidepressants benefited from this treatment. The most common AEs were somnolence and lack of perceived benefit, and no patient reported worsening of IBS symptoms. Despite the lack of controls in this study, the results can be considered encouraging because all subjects had severe IBS. The clinical benefit of quetiapine has also been described in some case reports [38,39]. Quetiapine-XR at 100 mg/d augmented with venlafaxine at 300 mg/d for 2 weeks led to rapid and notable improvement in abdominal pain and frequent defecation and eventually resulted in complete remission of IBS symptoms [38]. No studies evaluating the use of other AAs in IBS or other FGIDs have been performed. However, a larger, prospective, open-label study is currently underway by Dr. Drossman' group [40].

A variety of psychiatric conditions are commonly seen in patients with IBS, such as pain symptoms, depressive symptoms, early abuse history, anxiety symptoms and sleep disturbances [6,7,41,42]. These psychiatric symptoms are also considered to be important treatment targets in patients with IBS. In line with this perspective, it should be noted that aripiprazole, quetiapine and the combination of fluoxetine and olanzapine (Symbiax) have demonstrated clear efficacy and safety/tolerability in the treatment of MDD, and they have recently received an official indication as augmentation agents for MDD (quetiapine and aripiprazole) and treatment-resistant depression (Symbiax) [12,13].

Although, previous studies on AAs for the treatment of fibromyalgia were mostly uncontrolled case reports or small-scale open trials and mainly involved olanzapine, quetiapine, ziprasidone and amisulpride [43], a recent placebo-controlled pilot clinical trial showed a promising clinical benefit of quetiapine as add-on therapy in patients with fibromyalgia [44]. Risperidone, olanzapine and quetiapine have shown efficacy in the treatment of anxiety disorders. In particular, quetiapine has proven its efficacy over placebo for the treatment of generalised anxiety disorder (GAD) in a number of adequately powered controlled clinical trials [45], whereas currently available data on olanzapine and risperidone are still too limited to draw any conclusions. Monotherapy with quetiapine appears be efficacious in the reduction of GAD symptoms as early as week 1, and this effect should be comparable to that of antidepressants officially approved for the treatment of GAD [46].

In a placebo-controlled, randomised cross-over study of quetiapine that investigated the polysomnographic sleep structure and subjective sleep quality of 14 healthy subjects, quetiapine at 25 and 100 mg significantly improved sleep induction and continuity under standard and acoustic stress conditions [47]. Additionally, increase in total sleep time, sleep efficiency, percentage of time in sleep stage 2 and subjective sleep quality were seen. Similar results were also observed in placebo-controlled cross-over sleep studies with olanzapine [48] and ziprasidone [49] in healthy subjects.

5. Expert opinion

When we reflect that no universally effective agent has not been found today and consider the heterogenous and complex nature of the disorder, effective non-pharmacological treatment approaches such as construction of tight and reliable clinician-patient relationship, education and cognitive-behavioral therapy, should be first taken rather than biological treatment approach at the initial treatment phase. AAs may appear to have some potential for the treatment of some portion of IBS patients and thereby sparing the use of AAs only for such IBS population should be prudent.

In fact, despite there are numerous options for IBS treatment, approximately 15 – 20% of patients fail to respond adequately [50]. Overall, the management of IBS may require a multimodal treatment approach, including dietary and lifestyle modifications and effective pharmacological treatment for symptomatic control [6,8]. When the expected treatment response is not adequate, psychotropic medications including various antidepressants may be one of the next therapeutic regimens in the treatment of such patients IBS. In this regard,

Table 1. Potential action mechanism of atypical antipsychotics in irritable bowel syndrome.

Pharmacodynamic profile: serotonin and norepinephrine reuptake inhibition, dopamine and glutamate neurotransmission
Stabilisation of immune alteration: proinflammatory cytokine levels (i.e., TNF-α and IL-6)
Recovery of hypothalamic-pituitary-adrenal axis alteration
Alteration of intestinal motility (contraction): anticholinergic affinity, effects on dopamine (D2) receptors, histamine (H1) antagonism and 5HT 1A agonism
Regulation of neurotropins: brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF)
Regulation of gut flora (microbial)
Analgesic effect: opioid system, α2-adrenoreceptor
Therapeutic effects on mood symptoms and associated behavioral disturbance
Therapeutic effects on anxiety symptoms (including stress reaction) and associated behavioral disturbance
Improvement of sleep disturbance: improved sleep induction, increases in total sleep time, sleep efficiency, percentage sleep stage 2 and subjective sleep quality
Treatment of psychiatric comorbidities such as MDD, GAD, and fibromyalgia

GAD: Generalised anxiety disorder; IL: Interleukin; MDD: Major depressive disorder; TNF: Tumor necrosis factor.

Table 2. Tips for prescribing atypical antipsychotics for patients with irritable bowel syndrome (IBS).

No atypical antipsychotics (AAs) have been approved by authority agency for the treatment of IBS worldwide. All AAs should be off-label use for IBS
Based on currently available findings, the most information is available for quetiapine and olanzapine. Consider individual and differential pharmacological characteristics of AAs for patients with IBS (i.e., quetiapine and olanzapine for sleep disturbance and troubling agitation)
Justify AAs use for defining target symptoms among IBS symptoms in your patient
The target doses of AAs in IBS should be lower than those found to be efficacious in the treatment of major depressive disorder or generalized anxiety disorder (Minimal efficacious dose)
Trying AAs after routine treatment of IBS should be prudent rather than treatment at the beginning
Consider AAs as augmentation agents for partial responder to initial IBS treatment
Consider AAs for control of specific mood symptoms, anxiety, psychiatric comorbidities and associated behavioral disturbance which will be ameliorated by treatment with AAs
Need rigorous decision making whether the patients would need AAs based on risk and clear clinical benefits; periodic re-evaluation for AAs use should be followed as well
Need regular monitoring for the development of untoward adverse events by AAs (i.e., in particular, olanzapine for weight gain, quetiapine for sedation, aripiprazole for akathisia)
Discussion and education of patients for AAs treatment for IBS
Temporary use of AAs for IBS patients should be better than maintaining them upon symptomatic improvement

emerging evidence proposes the potential utility of AAs in the treatment of IBS. **Table 2** summarises some useful tips in prescribing AAs for patients with IBS.

AAs may have a role in the treatment of IBS based on the currently available findings. However, there is no clear evidence, and a number of clinical issues to be addressed in the use of AAs for the treatment of IBS. In fact, the American College of Gastroenterology evidence-based recommendations for the management of IBS placed antidepressants at grade Ib (strong evidence), whereas it does not yet include AAs as recommended treatment for IBS [11]. According to an anecdotal naturalistic study [51], the likelihood of remission of IBS symptoms was reduced in subsequent antidepressant trials after failure in an initial antidepressant trial involving patients with IBS, but limited data showed that a subsequent treatment approach with a different treatment regimen may be beneficial for such patients. For certain patients with IBS, AAs may be a viable next treatment option as augmentation agents in conjunction with current IBS treatments.

A previous preclinical study [20] indicated that individual AAs may exert differential analgesic effects via different mechanisms, and thus they are not identical in terms of analgesic effects [21]. For instance, risperidone was found to interact mainly with opioid receptors (mainly μ1-, μ2- and κ1-opioid receptor subtypes) [19], whereas clozapine interacted primarily with opioid receptors and α2-adrenoreceptors, but olanzapine mainly affects α2-adrenoreceptors [20,21]. The involvement of the neurotransmitter system is intricate and complex in the development and management of pain, although it is clear that neurotransmitters interact with one another in more than one way. Several studies showed that activation of dopamine lowered opioid analgesia and that dopamine receptor antagonists enhanced analgesia [19,52]. However, D1 receptors were not utilised for such antinociceptive effects in a preclinical study [52]. Pretreatment with either the selective D1 receptor antagonist or the D2 receptor antagonist resulted in conversion of hyperalgesia to an antinociceptive response produced by the dopamine D1 receptor agonist, whereas the effect of the D2 receptor agonist was significantly antagonised [19,52]. Serotonin is also involved in the afferent signalling from the GI tract to the brain [53]. Among the serotonin (5-HT) receptors, 5-HT3 and 5-HT4 appear to be particularly important [54,55] and are putatively targeted by investigational therapeutic agents. Additionally, transgenic mice lacking serotonin transporters exhibit abnormalities in colonic motor function, suggesting a possible role of serotonin transporters in the pathophysiology of IBS [56]. Further research is warranted to elucidate the association between the mechanism of action of AAs and involvement of their potential opioid receptors in antinociception and analgesia [19].

No AAs have been approved by the FDA for the treatment of IBS. Although some data appear to suggest that AAs may offer some benefit for patients with IBS, careful consideration is warranted because available information is very limited and inconclusive. There is currently insufficient evidence to make

specific recommendations about individual AAs. However, among AAs, the most information is available for quetiapine, followed by olanzapine. Available data suggest that the target doses of AAs in IBS appear in the lower ranges of those found to be efficacious in the treatment of MDD or GAD. For off-label use of AAs, clinical benefit and harm should be carefully considered in clinical practice. In a recent meta-analysis of off-label uses of AAs including 162 trials with efficacy outcomes and 231 trials with AEs [57], adult patients commonly experienced fatigue and sedation. Aripiprazole, quetiapine and ziprasidone were associated with extrapyramidal symptoms. Akathisia was more often associated with aripiprazole use, and weight gain was common with several AAs, a statistically significant difference among aripiprazole, quetiapine, risperidone and olanzapine was found. Olanzapine was particularly associated with weight gain [57], and the incidence of akathisia in three aripiprazole MDD trials was approximately four times (about 23%) higher than that (6%) seen in schizophrenia trials [12]. Individual AAs may also have potentially different AE profiles. An elevated risk of weight gain is commonly seen in all AAs. However, an olanzapine–fluoxetine combination is associated with more profound weight gain, whereas quetiapine presents more sedation compared with placebo [58].

It must be noted again that the current information for AAs in the treatment of IBS is only derived from small-scale, open-label studies and case reports. Well-designed, placebo-controlled short- and long-term trials with well-characterised patients are necessary to fully evaluate the potential benefit of AAs in IBS. Therefore, it is necessary that clinicians be familiar with the use of individual AAs and their potential AEs in patients with IBS. An individual patient's specific target symptoms, the effectiveness of other interventions, the value of modest symptomatic improvement, the individual's particular susceptibility to AEs, and the goals of care should be considered in the use of AAs in patients with IBS [57]. The most conservative and prudent AA use in patients with IBS should augment the effects of antidepressants or other treatment regimens for patients with inadequate response to current therapeutic agents.

Acknowledgement

This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A120004).

Declaration of interest

The authors have no conflict of interests with this paper.

Bibliography

1. Mertz HR. Irritable bowel syndrome. N Engl J Med 2003;349:2136-46
2. Chang FY, Chen PH, Wu TC, et al. Prevalence of functional gastrointestinal disorders in Taiwan: questionnaire-based survey for adults based on the Rome III criteria. Asia Pac J Clin Nutr 2012;21:594-600
3. Park DW, Lee OY, Shim SG, et al. The Differences in Prevalence and Sociodemographic Characteristics of Irritable Bowel Syndrome According to Rome II and Rome III. J Neurogastroenterol Motil 2010;16:186-93
4. Jones R, Lydeard S. Irritable bowel syndrome in the general population. BMJ 1992;304:87-90
5. Drossman DA, Sandler RS, McKee DC, et al. Bowel patterns among subjects not seeking health care. Use of a questionnaire to identify a population with bowel dysfunction. Gastroenterology 1982;83:529-34
6. Pae CU, Masand PS, Ajwani N, et al. Irritable bowel syndrome in psychiatric perspectives: a comprehensive review. Int J Clin Pract 2007;61:1708-18
7. Masand PS, Kaplan DS, Gupta S, et al. Irritable bowel syndrome and dysthymia. Is there a relationship? Psychosomatics 1997;38:63-9
8. Viera AJ, Hoag S, Shaughnessy J. Management of irritable bowel syndrome. Am Fam Physician 2002;66:1867-74
9. Ford AC, Talley NJ, Schoenfeld PS, et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut 2009;58:367-78
10. Creed F, Fernandes L, Guthrie E, et al. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. Gastroenterology 2003;124:303-17
11. Graham L. ACG releases recommendations on the management of irritable bowel syndrome. Am Fam Physician 2009;79:1108-17
12. Pae CU, Forbes A, Patkar AA. Aripiprazole as adjunctive therapy for patients with major depressive disorder: overview and implications of clinical trial data. CNS Drugs 2011;25:109-27
13. Pae CU, Sohi MS, Seo HJ, et al. Quetiapine XR: current status for the treatment of major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:1165-73
14. Singh P, Agnihotri A, Pathak MK, et al. Psychiatric, somatic and other functional gastrointestinal disorders in patients with irritable bowel syndrome at a tertiary care center. J Neurogastroenterol Motil 2012;18:324-31
15. McIntyre RS, Soczynska JK, Woldeyohannes HO, et al. A preclinical and clinical rationale for quetiapine in mood syndromes. Expert Opin Pharmacother 2007;8:1211-19
16. Caley CF, Cooper CK. Ziprasidone: the fifth atypical antipsychotic. Ann Pharmacother 2002;36:839-51
17. Dekel R, Drossman DA, Sperber AD. The use of psychotropic drugs in irritable bowel syndrome. Expert Opin Investig Drugs 2013;22(3):329-39
18. Camilleri M, Atanasova E, Carlson PJ, et al. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel

syndrome. Gastroenterology 2002;123:425-32

19. Weizman T, Pick CG, Backer MM, et al. The antinociceptive effect of amisulpride in mice is mediated through opioid mechanisms. Eur J Pharmacol 2003;478:155-9
20. Schreiber S, Getslev V, Backer MM, et al. The atypical neuroleptics clozapine and olanzapine differ regarding their antinociceptive mechanisms and potency. Pharmacol Biochem Behav 1999;64:75-80
21. Fishbain DA, Cutler RB, Lewis J, et al. Do the second-generation "atypical neuroleptics" have analgesic properties? A structured evidence-based review. Pain Med 2004;5:359-65
22. Seidel S, Aigner M, Ossege M, et al. Antipsychotics for acute and chronic pain in adults. Cochrane Database Syst Rev 2008(4):CD004844
23. Dome P, Teleki Z, Kotanyi R. Paralytic ileus associated with combined atypical antipsychotic therapy. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:557-60
24. Zuccato E, Bertolo C, Salomoni M, et al. The effects of S(-) and R(+) sulpiride, metoclopramide, cisapride and domperidone on the small intestine suggest DA2-receptors are involved in the control of small intestinal transit time in rats. Pharmacol Res 1992;26:179-85
25. Niddam DM, Tsai SY, Lu CL, et al. Reduced hippocampal glutamate-glutamine levels in irritable bowel syndrome: preliminary findings using magnetic resonance spectroscopy. Am J Gastroenterol 2011;106:1503-11
26. Tascedda F, Lovati E, Blom JM, et al. Regulation of ionotropic glutamate receptors in the rat brain in response to the atypical antipsychotic seroquel (quetiapine fumarate). Neuropsychopharmacology 1999;21:211-17
27. Dinan TG, Quigley EM, Ahmed SM, et al. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? Gastroenterology 2006;130:304-11
28. Sugino H, Futamura T, Mitsumoto Y, et al. Atypical antipsychotics suppress production of proinflammatory cytokines and up-regulate interleukin-10 in lipopolysaccharide-treated mice. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:303-7
29. Altschuler EL, Kast RE. Using histamine (H1) antagonists, in particular atypical antipsychotics, to treat anemia of chronic disease via interleukin-6 suppression. Med Hypotheses 2005;65:65-7
30. Yu YB, Zuo XL, Zhao QJ, et al. Brain-derived neurotrophic factor contributes to abdominal pain in irritable bowel syndrome. Gut 2012;61:685-94
31. Nandra KS, Agius M. The differences between typical and atypical antipsychotics: the effects on neurogenesis. Psychiatr Danub 2012;24(Suppl 1):S95-9
32. Severance EG, Alaedini A, Yang S, et al. Gastrointestinal inflammation and associated immune activation in schizophrenia. Schizophr Res 2012;138:48-53
33. Makikyro T, Karvonen JT, Hakko H, et al. Comorbidity of hospital-treated psychiatric and physical disorders with special reference to schizophrenia: a 28 year follow-up of the 1966 northern Finland general population birth cohort. Public Health 1998;112:221-8
34. Lapierre L, Undeland P, Cox LJ. Lithium chloride-sodium propionate agar for the enumeration of bifidobacteria in fermented dairy products. J Dairy Sci 1992;75:1192-6
35. Basta-Kaim A, Budziszewska B, Leskiewicz M, et al. Hyperactivity of the hypothalamus-pituitary-adrenal axis in lipopolysaccharide-induced neurodevelopmental model of schizophrenia in rats: effects of antipsychotic drugs. Eur J Pharmacol 2011;650:586-95
36. Cohrs S, Roher C, Jordan W, et al. The atypical antipsychotics olanzapine and quetiapine, but not haloperidol, reduce ACTH and cortisol secretion in healthy subjects. Psychopharmacology (Berl) 2006;185:11-18
37. Grover M, Dorn SD, Weinland SR, et al. Atypical antipsychotic quetiapine in the management of severe refractory functional gastrointestinal disorders. Dig Dis Sci 2009;54:1284-91
38. Martin-Blanco A, Pascual JC, Soler J, et al. Quetiapine in the treatment of refractory irritable bowel syndrome: a case report. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:715-16
39. Smith NL. Serotonin mechanisms in pain and functional syndromes: management implications in comorbid fibromyalgia, headache, and irritable bowl syndrome - case study and discussion. J Pain Palliat Care Pharmacother 2004;18:31-45
40. NCT00617396. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00617396?term=irritable+bowel+syndrome%2Cantipsychotic&rank=2 [Last accessed 15 January 2013]
41. Marks DM, Han C, Krulewicz S, et al. History of depressive and anxiety disorders and paroxetine response in patients with irritable bowel syndrome: *post hoc* analysis from a placebo-controlled study. Prim Care Companion J Clin Psychiatry 2008;10:368-75
42. Han C, Masand PS, Krulewicz S, et al. Childhood abuse and treatment response in patients with irritable bowel syndrome: a *post-hoc* analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release. J Clin Pharm Ther 2009;34:79-88
43. Calandre EP, Rico-Villademoros F. The role of antipsychotics in the management of fibromyalgia. CNS Drugs 2012;26:135-53
44. Potvin S, Morin M, Cloutier C, et al. Add-on treatment of quetiapine for fibromyalgia: a pilot, randomized, double-blind, placebo-controlled 12-week trial. J Clin Psychopharmacol 2012;32:684-7
45. Stein DJ, Bandelow B, Merideth C, et al. Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalised anxiety disorder: an analysis of pooled data from three 8-week placebo-controlled studies. Hum Psychopharmacol 2011;26:614-28
46. Depping AM, Komossa K, Kissling W, et al. Second-generation antipsychotics for anxiety disorders. Cochrane Database Syst Rev 2010(12):CD008120
47. Cohrs S, Rodenbeck A, Guan Z, et al. Sleep-promoting properties of quetiapine in healthy subjects. Psychopharmacology (Berl) 2004;174:421-9

48. Gimenez S, Clos S, Romero S, et al. Effects of olanzapine, risperidone and haloperidol on sleep after a single oral morning dose in healthy volunteers. Psychopharmacology (Berl) 2007;190:507-16

49. Cohrs S, Meier A, Neumann AC, et al. Improved sleep continuity and increased slow wave sleep and REM latency during ziprasidone treatment: a randomized, controlled, crossover trial of 12 healthy male subjects. J Clin Psychiatry 2005;66:989-96

50. Drossman DA, Camilleri M, Mayer EA, et al. AGA technical review on irritable bowel syndrome. Gastroenterology 2002;123:2108-31

51. Clouse RE, Lustman PJ, Geisman RA, et al. Antidepressant therapy in 138 patients with irritable bowel syndrome: a five-year clinical experience. Aliment Pharmacol Ther 1994;8:409-16

52. Rooney KF, Sewell RD. Evaluation of selective actions of dopamine D-1 and D-2 receptor agonists and antagonists on opioid antinociception. Eur J Pharmacol 1989;168:329-36

53. Kim DY, Camilleri M. Serotonin: a mediator of the brain-gut connection. Am J Gastroenterol 2000;95:2698-709

54. Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. Aliment Pharmacol Ther 1999;13(Suppl 2):15-30

55. Talley NJ. Review article: 5-hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation: clinical implications. Aliment Pharmacol Ther 1992;6:273-89

56. Chen JJ, Li Z, Pan H, et al. Maintenance of serotonin in the intestinal mucosa and ganglia of mice that lack the high-affinity serotonin transporter: abnormal intestinal motility and the expression of cation transporters. J Neurosci 2001;21:6348-61

57. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. Jama 2011;306:1359-69

58. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry 2009;166(9):980-91

Affiliation

Chi-Un Pae[†1,2], Soo-Jung Lee[1], Changsu Han[3], Ashwin A Patkar[2] & Prakash S Masand[4]
[†]Author for correspondence
[1]The Catholic University of Korea
College of Medicine,
Bucheon St. Mary's Hospital,
Department of Psychiatry,
2 Sosa-Dong, Wonmi-Gu, Bucheon,
Kyeonggi-Do 420-717, Republic of Korea
Tel: +82 32 340 7067;
Fax: +82 32 340 2255;
E-mail: pae@catholic.ac.kr
[2]Duke University Medical Center,
Department of Psychiatry and
Behavioral Sciences, Durham, NC, USA
[3]Korea University, College of Medicine,
Ansan Hospital, Department of Psychiatry,
Ansan, Kyounggi-Do, Republic of Korea
[4]Global Medical Education,
New York, NY, USA