Clinical overview

Augmentation of antidepressants with atypical antipsychotics for treatment-resistant major depressive disorder

Shelton RC, Papakostas GI. Augmentation of antidepressants with atypical antipsychotics for treatment-resistant major depressive disorder.

Objective: Atypical antipsychotics (AAPs) have been hypothesized to be beneficial in treatment-resistant depression (TRD). This paper will review a biochemical rationale and will summarize the data regarding the effectiveness of AAPs in TRD.

Method: Studies were identified using searches of Pubmed/Medline, EMBase and the Cochrane databases by cross-referencing the term ‘depression’ with each of the six AAPs.

Results: After initial positive, short case reports and clinical trials, larger studies failed to show the effectiveness of AAPs combined with antidepressants for TRD. More recently, larger scale clinical trials have supported the effectiveness of at least some of these medications. While AAPs have gained in popularity for TRD, there are nagging concerns regarding risks such as metabolic syndrome and tardive dyskinesia.

Conclusion: The existing research provides some support for the beneficial effects of AAPs when combined with SSRIs in TRD. These medications pose significant risks that must be considered in their use.

Clinical recommendations

- There are some data supporting efficacy for atypical antipsychotic augmentation of antidepressants in patients who do not fully respond to antidepressant monotherapy.
- The possible benefits for treatment resistance must be weighed in view of the attendant risks. All atypical drugs risk tardive dyskinesia. Weight gain and metabolic syndrome risk are elevated with a subset of drugs, including olanzapine and, to a lesser degree, quetiapine and risperidone.
- Ongoing monitoring of these risks is needed in clinical practice.

Additional comments

- Treatment-resistant depression is very common.
- The use of standardized rating instruments such as the Quick Inventory of Depressive Symptoms (1) (which is in the public domain and available online in multiple translations http://www.ids-qids.org/), the Zung Self-Rating Depression Scale (2), the Beck Depression Inventory (3), and others, will improve the ongoing evaluation of the response of depression.

Introduction

Available antidepressants have proliferated over the last 20 years. Newer antidepressant drugs, including the serotonin selective reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have gained wide acceptance, primarily because of their relative safety. However, expectations with regard to efficacy may be higher than the reality of clinical
practice. For example, the response rates reported for most newer antidepressant medications were in the range of 60–70% in placebo-controlled clinical trials (4). However, people who met the definition of response (typically 50% improvement on a depression scale) could still have significant functional impairment (5). However, far fewer patients achieve true remission [(6); e.g. a Hamilton Rating Scale for Depression (7) (HAM-D) score of ≤7]. This was highlighted in the recent National Institute of Mental Health Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (8). In this study that included more than 4000 patients, the initial remission rate with citalopram was remarkably low: 28% on the HAM-D and 33% on the Quick Inventory of Depressive Symptons, self-report version (QIDS-SR; 9). This was in spite of the fact that the mean dose of citalopram was relatively high at 41.8 mg/day (8). However, these results are consistent with those demonstrated in prior controlled trials (4). This indicates that only a minority of patients experience recovery with the first antidepressant treatment. Moreover, the majority of patients in STAR*D who achieved remission experienced relapse within the next year (10).

Aims of the study

The aims include the following: i) search the available clinical and basic literature for references to the atypical antipsychotics (AAPs) and references to the use of AAPs for depression; ii) review the putative pharmacological mechanisms of action relevant to treatment-resistant depression (TRD); iii) summarize research on the use of atypical antipsychotics in TRD; this includes the following drugs: olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole and iv) summarize the data with regard to effectiveness and risk of atypicals in TRD.

Material and methods

Studies were identified using searches of PubMed/Medline. Searches were conducted by cross-referencing the term ‘depression’ with each of the six following terms: ‘risperidone’, ‘olanzapine’, ‘quetiapine’, ‘ziprasidone’, and ‘aripiprazole’. No language or year of publication limits were used. These searches were then repeated using Embase and the Cochrane databases as well. We also searched the abstracts of major psychiatric meetings held since 2000 (American Psychiatric Association; New Clinical Drug Evaluation Unit of the National Institutes of Mental Health; American College of Neuropsychopharmacology; European College of Neuropsychopharmacology; Collegium Internationale Neuropsychopharmacologicum; Society of Biological Psychiatry, World Federation of Societies of Biological Psychiatry; World Psychiatric Association).

Mechanisms of action

Typical antipsychotics (e.g., haloperidol) appear to exert their effects mainly through dopamine 2 (D2) receptor blockade. By contrast, most AAPs are relatively weak D2 antagonists (11). Any benefit in mood disorders may relate to their effects on serotonin (5HT) receptors. All block 5HT2A and 5HT2C receptors. Aripiprazole and ziprasidone are also potent partial agonists at 5HT1A receptors. These effects confer a very different pharmacodynamic profile relative to classical drugs.

5HT2A receptor blockade produces a complex set of effects that are relevant to antidepressant actions. Antidepressant drugs like trazodone and nefazodone also block 5HT2A, which may contribute to their antidepressant and anti-anxiety properties (12). The blockade of these receptors, then, may help to deal with residual symptoms of depression or anxiety. However, in the presence of serotonin reuptake inhibition (i.e., enhanced serotonin availability), selective 5HT2A receptor blockade enhances the release of both serotonin and norepinephrine in rat brain (13).

Mechanistically, this difference appears to depend, at least in part, on the relative binding affinity to specific serotonin receptors. As an example, olanzapine is a modestly potent D2 antagonist (Ki = 11 nmol/l) and a significantly more robust 5HT2A blocker (Ki = 2.5; 14, 15). As well, the drug significantly inhibits 5HT2C, 5HT3, 5HT6, as well as norepinephrine (NE) alpha1, muscarinic cholinergic and histamine-1 receptors. Moreover, although the affinity is low for glutaminergic receptors, chronic administration has been shown to decrease NMDA and increase AMPA receptor labeling in the caudate and putamen (16). The profile of relatively weaker D2 and more potent 5HT2A antagonism has been proposed as an essential feature of AAPs (11, 17, 18).

This complex profile of receptor binding appears to affect dopaminergic systems quite differently than the typical drugs. The antipsychotic effects of drugs like haloperidol seem to be the result of simple antagonism at the D2 receptor. By contrast, AAPs weakly block the D2 receptor but also affect presynaptic dopamine release. Given the weak D2 receptor blockade coupled with increased synaptic dopamine yields competition for binding at dopamine receptors D2 blockade. This may reduce the
propensity for Parkinsonian side effects (18). Another complexity arises from the fact that D2 receptor blockade tends to enhance dopamine release. However, blockade of both 5HT2A (19) and 5HT6 (20) receptors, in the face of weak D2 receptor blockade enhances dopamine release to a greater extent than would be seen by blockade of either receptor alone. Beyond this, both norepinephrine and dopamine release is increased by both 5HT2C blockade (21) and 5HT1A activation (22) (as seen with zimaxidine and aripiprazole). The enhancement of norepinephrine and dopamine release in frontal cortex and nucleus accumbens would be expected to improve attention and motivation, common symptoms of depression. In addition, as SSRIs suppress the activity of locus ceruleus (the principal source of norepinephrine) (13) and ventral tegmental area (the origin of extrastriatal dopamine; 23, 24), the effect of atypicals on catecholamines might be expected to counterbalance this tendency.

The clinical effects of atypical antipsychotics in treatment-resistant depression

The neurochemical effects described above led to the initial testing of AAPs for cognitive and mood symptoms associated with schizophrenia (25). This subsequently led into the evaluation of AAPs for mood symptoms in treatment-resistant depression (TRD) and bipolar depression. For the purpose of this paper, TRD is defined as the failure of at least one adequate trial of an antidepressant. This section will review the data supporting effects of these drugs individually, and will focus, primarily, on controlled clinical trials.

**Olanzapine** The first controlled test of the effects of an AAP in TRD was a short study on olanzapine, which compared the effects of olanzapine as a monotherapy (i.e., olanzapine plus placebo), olanzapine in combination with fluoxetine, and fluoxetine as a monotherapy in TRD (26). All participants had previously failed adequate trials of an SSRI and a non-SSRI antidepressant, as well as a prospective treatment period with fluoxetine alone up to 60 mg/day. Non-responders \( (n = 28) \) to this run-in treatment were then randomly assigned to one of the three conditions in a double-blind fashion. The average maximum dose in the double-blind period for olanzapine alone was 12.5 mg/day, for fluoxetine alone was 52 mg/day, and for the combination of olanzapine and fluoxetine was 13.5 and 52 mg/day, respectively. The continuation of fluoxetine for this period yielded essentially no further improvement.

Olanzapine given alone achieved a modest benefit over fluoxetine, while the olanzapine plus fluoxetine combination resulted in significantly greater improvement in depressive symptoms than either monotherapy. Remission, defined as a 17 item HAM-D score of 7 or less, was achieved in 60% of patients taking the combination, 25% with olanzapine alone, and 20% with fluoxetine alone.

Two large-scale clinical trials testing the effects of the olanzapine plus fluoxetine combination were undertaken (27, 28). In the first, 500 patients were prospectively treated with nortriptyline (27); responders were excluded, leading into the double-blind phase. Patients were randomly assigned to one of four treatment groups for 8 weeks: olanzapine plus placebo, fluoxetine plus placebo, a combination of olanzapine plus fluoxetine, or a continuation of nortriptyline. Olanzapine was dosed in groups at 6–12 mg/day and fluoxetine 25–50 mg/day. The combination of olanzapine and fluoxetine produced a rapid effect relative to the other groups. However, the groups did not differ at endpoint. A number of design and execution factors may have affected these results. Patients had failed only one adequate trial of an SSRI prior to entry. The doses of both fluoxetine and olanzapine were lower than in the previous study: the mean maximal dose of olanzapine was 8.5 mg/day and fluoxetine was 36.5 mg/day. Further, the use of nortriptyline may have been problematic. Although the mean dose in the initial phase was sufficient (104.6 mg/day), many patients achieve their maximum dose relatively late in phase 1. Given the delay until maximum response to antidepressant treatment, the response to the dose achieved in phase 1 may have occurred early in phase 2. A second study using venlafaxine as a comparator was also negative, but suffered from many of the same design problems and will not be reviewed in detail (28).

There have been two subsequent studies that were designed in a way that was similar to the first olanzapine–fluoxetine trial (26, 29). In each, patients with at least one retrospective antidepressant failure were treated with fluoxetine. Those without response were randomly assigned to continuation of fluoxetine (plus placebo), olanzapine (plus placebo), or the olanzapine/fluoxetine combination. In one study \( (n = 638; 29) \), combination of olanzapine/fluoxetine produced no greater effect than either monotherapy. However, the fluoxetine monotherapy treatment produced a significant effect by the end of the study, indicating another failed trial. However, the second project \( (n = 675) \) (29) confirmed the more robust effect of combined olanzapine/fluoxetine in treatment-resistant depression.
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unipolar major depression compared with olanzapine or fluoxetine monotherapy. The pooled analysis of both of these studies also showed a significantly greater effect of the combination.

**Risperidone** The first published report of the effectiveness of an AAP in TRD was with risperidone (30). In this case series, eight patients who have failed to respond to an adequate trial of an SSRI were given risperidone in an open fashion, and all experienced a rapid benefit. However, there was no controlled clinical trial data with risperidone in TRD until recently. The first large scale clinical trial was intended to test the longer-term effects of a combination of an SSRI and risperidone (31). In this study, 489 patients with one to three prior documented treatment failures were treated prospectively with citalopram (20–60 mg) and risperidone (31). In this study, 489 patients were treated with an optimized trial of an SSRI alone in a post hoc fashion, and all experienced a rapid benefit. However, there was no controlled clinical trial data with risperidone in TRD until recently. The first large scale clinical trial was intended to test the longer-term effects of a combination of an SSRI and risperidone (31). In this study, 489 patients with one to three prior documented treatment failures were treated prospectively with citalopram (20–60 mg/day). Those who experienced ≥ 50% improvement were excluded. The remainder (n = 386) were given 4–6 weeks of open-label risperidone (0.25–2.0 mg/day) in combination with citalopram. Patients with 17-item HAM-D score of ≤ 7 or a clinical global impression severity scale (CGI-S) score of ≤ 2 (i.e., ‘much improved’ or ‘very much improved’) were randomized to risperidone or placebo augmentation (n = 243 remitters [63%], 241 randomized). The primary endpoint – time to relapse – did not differ between groups. The median time to relapse was 102 days with risperidone plus citalopram and 85 days with placebo plus citalopram. Relapse rates were 53.3% with the combination and 54.6% with continuation of citalopram alone. These data indicate that continuation of risperidone plus citalopram was not effective in preventing relapse compared with citalopram alone.

It should be noted that some aspects of this risperidone augmentation trial are curious. For example, the choice of a long-term relapse prevention trial without first establishing an acute benefit seems unusual. In addition, only 11.2% of patients treated acutely with citalopram achieved a 50% improvement on the HAM-D. This rate of response is unusually low, even in a treatment-resistant population. The authors do note that patients considered ‘fully non-responsive’ to citalopram (i.e., who achieved < 25% improvement on HAM-D), there was a significant relapse prevention effect of the combination relative to citalopram alone in a post hoc analysis.

In second controlled trial (32), 463 depressed patients were treated with an optimized trial of an antidepressant. The 274 patients who did not respond were randomized to receive risperidone, 1 to 2 mg/d, or placebo combined with the initial antidepressant for 6 weeks. Mean HAM-D scores reduced from 24.2 to 15.2 in the risperidone group and from 24.6 to 17.5 in the placebo group, a statistically significant difference.

In a third controlled trial, Keitner et al. (33) studied 97 outpatients who met DSM-IV criteria for a unipolar, non-psychotic major depressive episode and failed to fully respond to an adequate (i.e., 5-week trial) monotherapy trial. Patients were randomized to receive either adjuntive risperidone or placebo for a total of 4 weeks of treatment. The odds of remitting were significantly better for patients treated with adjuntive risperidone than placebo (52% vs. 24%, respectively).

**Quetiapine** Quetiapine has received approval by the U.S. FDA for bipolar depression as monotherapy (34). However, there are now three controlled trials in unipolar TRD. One study (35) evaluated the effects of quetiapine for SSRI/SNRI partial response in 40 patients. This was an 8-week, double-blind, placebo-controlled study in which patients were and were randomized 2 : 1 ratio to receive quetiapine 200–400 mg/day or placebo along with their previous SSRI/SNRI. Of quetiapine-treated patients, 21 of 26 (80.8%) completed the study compared with 11 of 14 (78.6%) of the placebo group. At the end of 8 weeks, the quetiapine group had significantly lower HAM-D17 scores than the placebo group (8.3 vs. 14.7) as well as higher responses (67% vs. 27%) and remission rates (43% vs. 15%).

In another study, McIntyre et al. (36) studied 58 patients who did not experience sufficient symptom improvement following adequate treatment with either an SSRI or venlafaxine. Patients were randomized in a double-blind fashion to either receive adjuntive treatment with quetiapine or placebo for a total of 8 weeks. Eighteen of 29 quetiapine-treated and 16 of 29 placebo-treated patients completed the study. A greater resolution of depressive symptoms was reported among patients treated with adjunctive quetiapine than placebo (the mean difference in the reduction in HAM-D scores during treatment was 5.7 points in favor of quetiapine, P < 0.01).

Finally, in a third trial, Khullar et al. (37) studied 15 outpatients with TRD (to SSRIs or SNRIs, who underwent augmentation with either quetiapine or placebo for a total of 8 weeks. Quetiapine was more effective in reducing depressive symptoms than placebo (37% of patients remitted following adjutantive treatment with quetiapine, while none remitted following treatment with placebo).
Ziprasidone The basic pharmacology of ziprasidone is relatively unique and suggests possible benefit in TRD. In addition to being a D2/5HT2A/5HT2C antagonist, it is also a potent partial agonist of 5HT1A receptors (38). This would be expected to produce anti-anxiety effects in a way that is similar to buspirone. However, 5HT1A agonists also facilitate frontal dopamine and norepinephrine release (22, 39). Furthermore, it is also a potent reuptake inhibitor of norepinephrine and serotonin (38). The 5HT1A and monoamine transporter effects may account for the early activation seen with this medication, particularly at lower doses.

An initial open trial supported the effects of ziprasidone in TRD. In this study, 20 patients who had an incomplete response to a trial of an SSRI were treated with ziprasidone in an open fashion (40). Thirteen (65%) completed the trial; of this group eight (61.5%) were responders, as defined by a 50% improvement in HAM-D (17 item) score. Of all randomized, 10 were responders (50.0%), and 5 remitted (25.0%).

In a randomized, open study, adult outpatients who had not responded to a prior trial with an antidepressant were treated prospectively with sertraline, sertraline plus ziprasidone (80 mg/day: mean dose 78 mg/day), or sertraline plus ziprasidone 160 mg/day (mean 129.9 mg/day), for 8 weeks. The mean change from baseline was greater in the two ziprasidone augmentation groups (80 mg/day: −5.98 points; 160 mg/day: −8.27) than in the sertraline monotherapy group (−4.45), although this did not achieve statistical significance. Response rates were 19%, 32%, and 10%, and remission rates were 5%, 21%, and 5%, respectively. Although suggestive of possible benefit, these results were not conclusively in support of ziprasidone augmentation.

Aripiprazole Relatively little research has been done with Aripiprazole for TRD, and all reports to date have been short, open augmentation trials and retrospective chart reviews (42–46). In one, 12 patients who had failed to experience a sufficient response to an adequate trial of an SSRI, were treated with adjunctive aripiprazole in an open fashion for 8 weeks. Nine patients (75.0%) patients completed the trial; 5 (55.6%) achieved response (mean change in HAM-D score ≥ 50%), while 7 of the total group (58.3%) responded.

Discussion

Of the currently available AAPs in the U.S., olanzapine and quetiapine have strongly supportive data from prospective, controlled clinical trials as augmenters of SSRI’s for TRD. Although there is one positive controlled trial with risperidone, the data are not robust (32), and another longer-term outcome study was negative (31). The research supporting the augmentation effects of aripiprazole and ziprasidone are much more limited, and consist of short, open casereviews (40, 42–47) and, in the case of ziprasidone, one medium-sized open prospective trial in which ziprasidone plus sertraline was not statistically significantly better than sertraline alone (41). Therefore, although the data are supportive, they are decidedly mixed, and it remains unclear where they belong in a treatment algorithm.

Significant adverse effects pose problems; for example, weight gain and accompanying metabolic syndrome are associated with some, including olanzapine, clozapine, quetiapine, and risperidone. Moreover, all have the potential for inducing tardive dyskinesia (48). Although this risk is lower than with typical antipsychotics, the risk remains and has to be taken into consideration in using these drugs. Hyperprolactinemia also is a potential problem, particularly for risperidone (49), although elevations are seen at higher doses with olanzapine (50) and at least transiently with ziprasidone (51). Hence, although AAPs may be effective augmenters, their place remains obscure. Should they be used in the early stages of treatment? Probably not, given the potential for serious side effects. However, none have been tested systematically in more advanced TRD, i.e. when there have been multiple prior treatment failures. Tests of AAPs in advanced resistance are needed before their place in the treatment armamentarium is secured.

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