Augmentation With Atypical Antipsychotics

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By Gordon Parker, MD [2]

Clinical observations have shown that patients who do not respond to antidepressants may show dramatic improvement if atypical antipsychotics are added to their regimen. How can successful patient outcomes be maximized?

My experience of 15 years in a tertiary referral mood disorders unit has validated many recent studies suggesting that resistance to antidepressant treatment is more common than previously judged or conceded. About four years ago, I commenced testing augmentation of antidepressant drugs with atypical antipsychotics in treatment-resistant subjects and observed dramatically rapid improvement in a percentage of my patients. I have since learned that other psychiatrists have come to a similar conclusion by a similar testing process. This should not be viewed as necessarily challenging the zeitgeist of evidence-based treatment guidelines and consensus statements as the gold standard, but should encourage discussion as to how formalized efficacy data and clinically observed effectiveness data may best complement each other.

I observed two distinct improvement patterns in those patients who responded to the augmenting strategy. The first group of patients described a rapid improvement in mood, often in response to a low-dose atypical (e.g., olanzapine [Zyprexa] 2.5 mg to 5 mg) and generally in close association with restoration of sleep and a reduction in any anxiety symptoms. Improvement in these patients was usually evident in one to three days. Once improvement had occurred and patients were euthymic, the atypical could generally be ceased after another day or two, allowing the antidepressant and/or mood-stabilizing medication as the only necessary maintenance strategy -- at least, until any future episode.

In a second group of subjects, there was a slow and generally incomplete remission. There was a specific augmenting effect, since the patient would usually report a worsening of mood if the atypical was ceased. When the atypical was recommenced, the patient would again generally report partial benefit. In such patients, a higher dose of the atypical was generally required.

I was unable to find any treatment or practice guidelines advocating the use of antipsychotic or neuroleptic drugs for the management of depression, although one review suggested that the older antipsychotic drugs had antidepressant properties. Robertson and Trimble (1982) had evaluated more than 30 double-blind trials of typical antipsychotics, which were generally compared with a tricyclic or irreversible monoamine oxidase inhibitor antidepressant drug. Thus, their review did not consider typical neuroleptics as augmenting agents only as singleton antidepressants in head-to-head comparisons with antidepressant drugs. Their review data indicated that the antipsychotics were just as effective as the antidepressants, appeared comparatively free of side effects and tended to have an earlier onset of action. It is of interest that this antidepressant potential of antipsychotic drugs has been ignored in formal treatment guidelines, perhaps reflecting concerns about side effects of the older antipsychotic drugs, particularly tardive dyskinesia.

My colleague and I elected to write up a case series of two dozen non-psychotic patients treated with an atypical antipsychotic (Parker and Malhi, 2001). However, journal assessors were critical of case series data and judged that only a randomized, controlled treatment study was acceptable. Our paper, in which we described clinical features and considered the possible psychopharmacological rationale for atypicals, was eventually published.

In a case series report, Ostroff and Nelson (1999) described eight non-psychotic responders to a selective serotonin reuptake inhibitor remitting within one week of risperidone (Risperdal) augmentation. In 2001, Shelton et al. reported a controlled study whereby a small number of subjects with recurrent, non-psychotic, treatment-resistant depression were randomly assigned to receive olanzapine alone, fluoxetine (Prozac) alone, or the two drugs in combination. The combination produced significantly greater improvement than either monotherapy strategy over the next eight weeks, with the combination therapy being associated with a very rapid improvement in mood state. This report is the only published randomised, controlled trial examining the impact of...
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... atypical antipsychotic and hopefully will encourage studies of other atypical drugs as augmenting agents.

Atypical augmentation is now being built into treatment recommendations and guidelines. While Trivedi and Kleiber (2001) included the theoretical combined use of an antidepressant and an antipsychotic, Fava (2001) noted the positive reports of the combination of an antidepressant and an atypical in reviewing strategies for managing treatment-resistant depression.

Can we add to the story? Perhaps by offering more clinical impressions. Our observations suggest that patients with narrowly defined melancholic depression (particularly when their depression is marked by psychomotor disturbance) are more likely to receive augmenting benefit. Patients with bipolar disorder also appear highly likely to respond. Thus, not only did some of our patients with established bipolar disorder describe "riding a high" out of their depression -- but several patients who had never previously responded did so following atypical initiation. Our patients did not always report this improvement, so clinicians may need to probe for this information. When a severely depressed patient improves rapidly, both the patient and the physician may judge it as a rapid return to an euthymic state and miss features indicative of a "high." In such patients, these "highs" are generally slight and transient, but can be dissected from abrupt euthymia. This might suggest that atypicals act on the putative "switch" mechanism.

In a refined observational study, I treated 10 consecutive patients with treatment-resistant melancholic depression with olanzapine augmentation and monitored improvement over the next week (Parker, 2002). Six patients showed rapid and substantive improvement over that brief interval. This study is informative in that daily ratings of mood, anxiety, insomnia and depression identified differential effects across those parameters. Thus, these six patients showed dramatic improvements in insomnia and anxiety, while their depression improved somewhat more slowly. Such results raise the possibility that atypicals might be of benefit merely because they restore sleep, but most patients contemplating that possibility with me have generally rejected it on the basis that mood improvement occurs somewhat more slowly than sleep and anxiety benefits.

I began seeking views of other clinicians, expecting few to have tried such an augmentation strategy. The majority of clinicians I consulted also reported positive results using atypicals as augmenting agents. It has now become quite rare for us to see a treatment-resistant patient at our tertiary referral service who has not been tried on an atypical antipsychotic prior to our assessment. In the last decade there have been major advances in newer antidepressants. Each advance has emerged after careful evaluation involving controlled studies of large samples and up to a decade in investigation time. Following introduction of each drug, clinicians seek to understand their clinical effectiveness (as against their tested efficacy) and generally develop some gradual understanding about each drug's profile and, more important, the comparative benefits and situations where the drug might be recommended. This is obviously a slow process, respecting the scientific paradigm. By contrast, the augmentation story overviewed here is extraordinary. We now have atypical antipsychotic drugs -- that lack an indication as either antidepressants or as antidepressant-augmenting drugs -- being widely used by psychiatrists when the published literature comprises only one controlled study and two case series.

Quo vadis? We need to be very cautious in using atypical antipsychotics as either antidepressant drugs (unsupported at the moment) or as augmenting antidepressant agents (the presumptive strategy) until clarification studies accrue. We need to establish that true augmentation occurs and is not merely a reflection of an anxiolytic phenomenon, or there is a risk that these antipsychotics may be used for patients who have a primary anxiety disorder, as occurred with the typical antipsychotic drugs in the past. Even if atypicals are beneficial, we must be aware of both immediate and long-term side effects, which must be respected in cost-benefit decisions. Since we do not know the long-term side effects of these drugs, great caution needs to be exerted, particularly when used on an ongoing basis. We need to establish whether there is an intra-class differential or whether there is a non-specific class augmentation benefit and if there is depression subtype specificity when we hypothesize that melancholic and bipolar depression is preferentially responsive.

My observations suggest that augmentation by an atypical requires a potentially effective antidepressant to be augmented, a situation generally not readily judged in advance. Thus, I have seen patients who failed to benefit from augmentation while receiving an SSRI or a selective norepinephrine reuptake inhibitor but, when the antidepressant drug has been substituted with a TCA or an irreversible MAOI, have shown an almost immediate response. We need to establish if augmentation can be rapidly tapered or ceased in those patients who have returned to a euthymic state and, conversely, those situations that might determine a true need for an ongoing augmenting strategy. Finally and most important, we need to understand the biological rationale for such an
Augmentation phenomenon, as it may provide us with a greater understanding of the perturbations underpinning bipolar disorder and melancholic depression in particular.

**References:**


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