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**Some weight gain  
may be a necessary  
correlate of  
improvement  
in persons treated  
with antipsychotics**

# Adverse drug effects

## An upside to the downside?

Medication side effects are generally regarded as the Achilles' heel of pharmacologic treatment. And who can argue with that? Adverse effects are the downside of drug treatment of psychiatric disorders and are blamed for tolerability and adherence problems. Patients dread side effects, physicians feel uncomfortable or even guilty about them, and litigation lawyers thrive on them.

Psychotropics' package inserts are loaded with side-effect descriptions. The precautions, warnings, and black boxes frequently make patients anxious about taking medications, even when the diseases they suffer from pose far greater risk to their lives and health.

Are side effects entirely bad, or is there a possible upside lurking within them? Psychiatrists know, for example, that a common adverse effect of selective serotonin reuptake inhibitor (SSRI) antidepressants/anxiolytics is delayed orgasm. But because of this side effect, SSRIs can be dramatically helpful for treating premature ejaculation in nondepressed men.

Let's consider some effects of atypical antipsychotics that usually are considered a downside of antipsychotic treatment yet appear to be associated with advantages for the same patients.

### Therapeutic sedation

Sedation was considered a major adverse effect of quetiapine when this antipsychotic was approved for treating schizophrenia. Yet with time—and as the drug received additional indications for bipolar mania and bipolar depression—it became apparent to psychiatrists that quetiapine's sedative effects could be useful for treating insomnia in individuals with psychotic and mood disorders. Thus, practitioners saw an advantage in using a sedating antipsychotic, instead of adding a sedative/hypnotic, for psychotic or manic patients suffering from agitation, anxiety, and insomnia. Three advantages of this approach for patients are:

- fewer medications to manage
- lower costs without an additional sedative/hypnotic

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- avoiding the potential addictive effects of a sedative/hypnotic.

### Hyperprolactinemia and myelin repair

Some patients receiving risperidone or paliperidone for psychotic symptoms develop sexual dysfunction because of the side effect of increased serum prolactin. On the other hand, recent research indicates that prolactin enhances the synthesis of oligodendrocytes, which are critical for myelin (white matter) integrity in brain tissue.

In a recent study, researchers used a toxin to destroy patches of white matter in the brains of nonpregnant mice. Subsequent pregnancy and prolactin elevation repaired the myelin lesions completely, whereas no changes occurred in the white matter lesions in the brains of control mice that remained nonpregnant.<sup>1</sup>

This suggested myelin-repairing property of prolactin is highly relevant to the development of potential therapies, not only for demyelinating disorders such as multiple sclerosis but also for schizophrenia. Numerous studies have demonstrated that schizophrenia is associated with serious white-matter pathology,<sup>2</sup> which may account for many of the disorder's thought, emotional, and cognitive impairments.

### Weight gain as marker for antipsychotic efficacy

Some weight increase is observed with all antipsychotics, although certain atypicals such as olanzapine and clozapine are associated with more weight gain than others. No clinician would see anything except a

downside to weight gain, which may lead to metabolic complications such as diabetes, hyperlipidemia, and hypertension.

However, some weight gain appears to be related to the efficacy of all antipsychotics (first- and second-generation), according to the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)<sup>3</sup> and previous sporadic observations in the literature. Even Kraepelin noted in the 1920s—long before the era of antipsychotics—that patients with psychosis gained weight when they spontaneously improved.

Thus, some weight gain appears to be a necessary correlate of improvement in persons treated with antipsychotics. The reasons are still unclear, but weight gain may be a modulator, mediator, or marker of antipsychotic efficacy.

In summary, there appears to be at least some upside to the downside of certain drug side effects. In other words, every dark cloud has a silver lining, and it might be helpful for patients and physicians to see more than just the cloud.



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