Appendix D: Off-Label Use of Antipsychotics

Abilify, an atypical antipsychotic, has been the number one prescription drug in America for several years based on dollar-volume.\(^\text{281}\) Sales are $6.29 billion per year. But treatment of psychosis is not what made Abilify the top-selling drug in the United States. Abilify is now widely prescribed as an adjunctive drug for depression; and it is prescribed off-label for many uses.

The manufacturer says Abilify is indicated for:
- Use as an add-on treatment to an antidepressant for adults with Major Depressive Disorder who have had an inadequate response to antidepressant therapy
- Treatment of manic or mixed episodes associated with Bipolar I Disorder in adults and in pediatric patients 10 to 17 years of age
- Treatment of schizophrenia in adults and in adolescents 13 to 17 years of age
- Treatment of irritability associated with Autistic Disorder in pediatric patients 6 to 17 years of age

The use of Abilify as a multi-purpose drug is part of a larger trend toward use of antipsychotics. Antipsychotic use in the U.S. increased from 6.2 million treatment visits in 1995 to 14.3 million visits by 2008. This was accompanied by a shift from typical agents (often called neuroleptics, although this term is now deprecated), which accounted for 84% of all antipsychotic visits in 1995, to atypical agents, which accounted for

93% of visits by 2008.\textsuperscript{282} Many prescriptions for these drugs are for off-label uses. Overall, antipsychotic use for indications without FDA approval have more than doubled, from 4.4 million visits in 1995 to 9.0 million in 2008, with an astonishing 63% of uses now off-label.

The perception among prescribers is that the newer drugs (like Abilify and Invega) are well-tolerated and fairly benign, with few side effects and good efficacy for control of moods. As long-term experience with the newer drugs has accrued, however, some serious and distinct adverse effects of atypicals have come to light. Atypical antipsychotics cause significant weight gain\textsuperscript{283} and bring a higher risk of diabetes and other metabolic sequelae than their typical counterparts.\textsuperscript{284} Compared to nonusers, atypicals bring an increased risk of mortality and cardiovascular events in elderly patients with dementia.\textsuperscript{285} What's more, current comparative evidence suggests no definitive differences in efficacy, nor in net adverse effect profiles, between these two drug classes,\textsuperscript{286} calling into question


\textsuperscript{285} Gill \textit{et al.} (2007), "Antipsychotic drug use and mortality in older adults with dementia," \textit{Ann Intern Med}. 2007 Jun 5; 146(11):775-86. Online: \url{http://psychrights.org/research/digest/nlps/AmCollPhysicians6-5-07neurolepticskilledelderly.pdf} (retrieved 16 Jan. 2015). There was a 31% increased risk of death in 30 days, across the study population of 27,259 matched pairs of older patients. The RAND study (see footnote below) cites a hazard ratio of 1.54 (54% increased death risk) for a meta-analysis of 15 dementia treatment trials.

\textsuperscript{286} Sikich \textit{et al.} (2008), "Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS)
the wisdom of using atypicals for primary management of psychosis symptoms. A 2009 article in *Lancet* went a bit further, putting it this way:

> [T]he second-generation drugs have no special atypical characteristics that separate them from the typical, or first-generation, antipsychotics. As a group they are no more efficacious, do not improve specific symptoms, have no clearly different side-effect profiles than the first-generation antipsychotics, and are less cost effective. The spurious invention of the atypicals can now be regarded as invention only, cleverly manipulated by the drug industry for marketing purposes and only now being exposed.²⁸⁷

How good is the evidence for adjunctive use of atypical antipsychotics for management of depression? A RAND study for the U.S. Dept. of Health and Human Services found: "For SRI-resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone at 8 weeks."²⁸⁸ (Here, RAND uses SRI for "serotonin reuptake inhibitor" in place of the industry-standard term SSRI.)

With regard to its adjunctive use for depression, the Abilify website²⁸⁹ presents a synthesis of three studies, showing an average drop of 3.2

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points in patients' Montgomery–Åsberg Depression Rating Scale (MADRS) scores after 6 weeks of treatment, beyond the 6.2-point drop that occurs with placebo alone. (I was able to find two of the studies, one of which showed a 3-point drop, the other of which showed a less than 3-point drop.) The studies show that most of the benefit attributable to Abilify can be accounted for by placebo effect, but beyond that, there’s the question of whether an additional 3.2-point drop in a MADRS score is clinically significant. This represents the kind of drop you could get by changing your answer to one question on the MADRS survey (for example, if you’re sleeping better). It’s a very minimal change.

How good is the evidence for Abilify’s use in maintenance (ongoing) treatment of bipolar illness? Not good at all. A report by Tsai et al. (2011) said:

We systematically searched multiple databases to identify double-blind, randomized controlled trials of aripiprazole for the maintenance treatment of bipolar disorder while excluding other types of studies, such as open-label, acute, and adjunctive studies. We then used a citation search to identify articles that cited these trials and rated the quality of their citations. Our evidence search protocol identified only two publications, both describing the results of a single trial conducted by Keck et al., which met criteria for inclusion in this review. We describe four issues that limit the interpretation of that trial as supporting the use of aripiprazole for bipolar maintenance: (1) insufficient duration to demonstrate maintenance efficacy; (2) limited generalizability due to its enriched sample; (3) possible conflation of iatrogenic adverse effects of abrupt medication discontinuation with beneficial effects of treatment; and (4) a low overall completion rate. Our citation search protocol yielded 80 publications that cited the Keck et al. trial in discussing the use of aripiprazole for bipolar maintenance.

In other words, the use of Abilify for maintenance treatment of bipolar is supported by a single low-quality study, which has been extensively referenced by other papers in the literature. Of the 567 participants of the Keck study who entered the stabilization phase, only 206 com-
pleted it— a dropout rate of 74% for that phase of the study. As Tsai et al. explain: "This means that 361 of the 567 (74%) participants who entered the stabilization phase but dropped out were excluded from randomization because of adverse events, lack of efficacy, withdrawal of consent, and other reasons as detailed in the publication— leaving behind a selected group of participants who had responded favorably to aripiprazole in the stabilization phase to be subsequently randomized. This design could have the effect of biasing the trial’s findings away from the null, and, even in the absence of such bias, the results from this enriched sample cannot be generalized to the majority of persons diagnosed with bipolar disorder." But it's actually worse than that. Only seven Abilify-treated participants completed the full 100-week Keck trial, for a completion rate among Abilify-treated participants of under 1.3%.  

You can understand what would happen if you conducted a clinical trial of, say, a new weight-loss diet (perhaps a no-carbohydrates diet) and 70% of people in the treatment arm dropped out of the study. The people who dropped out would likely be the ones who lost no weight (or gained weight), became discouraged, and gave up on the diet. Those who stayed in the study would be much more likely to show that the diet is "efficacious." This is the problem with the Keck study mentioned above. It's a problem with many drug studies.

The evidence base for Abilify's use even in approved indications (other than the main indication: schizophrenia) is quite scanty. A better word would be shabby.

Before using these drugs, you might want to ask yourself whether the weight gain and diabetes risks are worth it. The RAND study (mentioned further above) found:

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Of Two Minds

- In two pooled RCTs of dementia patients, olanzapine (Zyprexa) users were 6.12 times more likely to report weight gain than placebo users.
- In a head-to-head trial of dementia patients, olanzapine users were 2.98 times more likely to gain weight than risperidone patients.
- In two pooled RCTs for depression with psychotic features, olanzapine patients were 2.59 times as likely as those taking conventional antipsychotics to report weight gain.
- Across seven studies of Tourette's and autism, users of Risperdal were 5.94 times more likely to report weight gain.

How much weight gain is "weight gain"? The standard used varies by study, but the industry consensus is that a 7% gain in BMI or body mass qualifies as a "weight gain" side effect.

It should be noted that Zyprexa and Clozaril are well established as the absolute worst offenders for weight gain and diabetes risk. No one in the industry seriously questions this (or the fact that all antipsychotics cause some weight gain). In depression sufferers, Zyprexa brings an 11-fold increased risk for weight gain. Gains of two pounds per month are common (although frankly, many people do worse than this). Two pounds a month may not sound like much until, at the end of the year, you're wondering why you weigh 24 pounds more.

You're also looking at stroke risk. According to the RAND study, risperidone (Risperdal) was associated with a greater than three-fold increased risk of cerebrovascular accident (stroke) compared to placebo, in elderly patients. The risk is equivalent to one extra stroke for every 31 patients studied.

These drugs also, as a class, bring extra risk of extrapyrimidal symptoms. These symptoms include dystonia (continuous spasms and muscle contractions), akathisia (general motor restlessness), Parkinsonism (characteristic symptoms such as rigidity, bradykinesia, and tremor), and tar-
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drive dyskinesia (irregular, involuntary, jerky movements, particularly of the mouth and tongue). The RAND study found that in elderly patients, Abilify and Risperdal brought a more than 2.5-fold increased risk of such symptoms, with a number-needed-to-harm of 16 for Abilify and 13 for Risperdal. Geodon was found to bring a more than 3-fold increased of extrapyrimidal symptoms in depression patients (who were not all elderly). Zyprexa and Risperdal were found to have 6 to 12 times the risk of extrapyrimidal symptoms compared to Seroquel.

Risperdal is well known to cause an increase in prolactin and associated breast enlargement (in men as well as women), sometimes associated with nipple discharge (in men and women). Reports of this are all over the Internet.

As an anecdotal aside, my wife is an experienced users of most of these drugs. She found that Zyprexa, while an excellent antipsychotic, does cause massive weight gain. She tried Geodon but had to discontinue it because of severe adverse psychotic symptoms. Her experience with Abilify and Saphris has been that both are effective for the positive symptoms of schizophrenia, but not effective enough in terms of suppressing paranoia; she needs an adjunctive dose of another antipsychotic (such as Haldol) for that. Haldol has proven to be a powerful, effective antipsychotic for my wife, but it brings significant weight gain and extrapyrimidal symptoms (akathisia in particular). So far, my wife has been lucky in avoiding tardive dyskinesia.

Latuda (which was too new to be included in the excellent RAND study) proved to be a terrible drug for my wife, producing hardened states of suicidality and dysphoria. It may well be an appropriate drug for schizophrenia proper, but for my wife (who suffers schizoaffective disorder), it was not a good choice.

The bottom line is: These are powerful drugs with serious side effects. They should not be taken (nor prescribed) haphazardly. Their usefulness in off-label indications is not well established, and the perception that the newer antipsychotics are more benign and more useful than the
older ones is not well founded. Unless you are suffering from florid psychosis, you should avoid all of these drugs if at all possible.