A n issue of the Psychiatric Annals devoted to generics? In an era when yesterday’s racemate is replaced by today’s left-handed isomer, it is rare to find coverage of medications that have no sponsor. The idea for Underutilized Treatments germinated from years of supervising psychiatry residents in their outpatient clinics at Rush University Medical Center in Chicago. Their quizzical looks at the mention of tricyclics or monoamine oxidase inhibitors (MAOIs), in contrast to their confidence in prescribing the (arguably more toxic) atypical antipsychotics, serve as an inspiration for this theme issue.

Another inspiration comes from conventional wisdom, passed down to yet another generation of fledgling psychopharmacologists. A postgraduate year-2 (PGY-2) tells me that “Buspar doesn’t work,” or “I would never give a tricyclic to a suicidal patient” and “Trazodone is only useful for sleep.” These were things I took for granted, too, gleaned from attendings, senior residents, and industry-sponsored journals when I was a resident 10 to 15 years ago.

In the era of evidence-based medicine, there’s no longer respect for rumors, clinical pearls, or unsubstantiated assertions. In the era of evidence-based medicine, there’s no longer respect for rumors, clinical pearls, or unsubstantiated assertions. Lithium, a drug that is lethal in overdose yet now a choice agent for suicidal patients with mood disorders, was considered a historical relic when I was a resident. Perhaps other decades-old treatments might be worthy of consideration. I became curious, and encouraged my resident supervisees to be curious as well.

Dr. Raatjes collaborates with me in our investigation of trazodone, the “forgotten” antidepressant (see page 148). Conventional wisdom is that few can tolerate trazodone at the heroic doses required for antidepressant efficacy. A review of the evidence suggests otherwise. Dr. Raatjes painstakingly reviews each comparative study he can find and concludes that trazodone is tolerated better than the tricyclic antidepressants (TCAs). It is distinguished from second-generation antidepressants by the type of its side effects rather than by overall tolerability. We also address the few studies of its use in insomnia, anxiety, and pain, as well as for geriatric patients.

With the widespread coprescribing of selective serotonin reuptake inhibitors (SSRIs) and trazodone (the latter, alas, for sleep), there is probably no recipe for the serotonin syndrome as commonly employed. We review the few case reports on serotonin syndrome and infer (from their dearth) that trazodone, by way of 5HT2A receptor antagonism, is unlikely to cause serotonin syndrome in low doses when combined with SSRIs. We also discuss the clinical utility of the new extended-release formulation of trazodone.

Our chief resident at Rush, Dr. Aaron Plattner, chose the TCAs as the subject of a grand rounds presentation (see page 158). As he prepared for the talk, he made some interesting discoveries. How many of us knew that nortriptyline (but not fluoxetine) is as effective as bupropion for smoking cessation? Or that clinical trials demonstrate equal tolerability between secondary TCAs and SSRIs? We find little evidence that TCAs are associated with a higher risk of suicide attempts or completed suicides as
compared with other antidepressants. We argue that there are still no antidepressants as versatile as TCAs for a range of psychosomatic disorders, including irritable bowel syndrome, headache, and idiopathic pruritus. These findings, and more, are discussed in our article on the tricyclics.

“Buspar doesn’t work” is a refrain heard at all levels of training. Many of us believe it has no side effects, either. With the FDA approval of vilazodone, an SSRI that is also a serotonin (5HT) 1a receptor partial agonist, a question that will arise is whether one can get the same benefit more affordably by combining buspirone (also a 5HT1a partial agonist) with an SSRI.

Drs. John Egger and Charles Hebert tackle these issues in their piece, “Buspirone: Anxiolytic, Antidepressant or Neither?” (see page 166). In pursuit of answers, they dig up dozens of articles published before the age of the Internet and electronic journals. They offer a mixed picture, with some studies finding buspirone as efficacious as, and others finding it inferior to, a range of treatments for generalized anxiety disorder (GAD). Is it a useful augmentation agent for depression? In phase 2 of the Sequential Treatment Alternatives to Relieve Depression (STAR*D) trial, buspirone was compared with bupropion as add-on therapy for patients whose depression had failed to remit after 12 weeks of citalopram. Despite equal efficacy, buspirone was associated with significantly more drop-outs due to self-reported side effects than bupropion. Drs. Egger and Hebert conclude, although not explicitly, that buspirone remains a drug in search of a cause.

Dr. Virginia O’Brien takes a second look at the monoamine oxidase inhibitors (MAOIs) and successfully argues that these drugs ought not be as daunting as commonly feared (see page 176). With lower tyramine levels in the national food supply and simplified dietary restrictions, hypertensive crises are much less likely now than in the 1960s. Dr. O’Brien compares the various MAOIs, including the selegiline transdermal system, and addresses the management of their side effects. She also discusses the use of psychostimulants and TCAs as augmentation agents. An important lesson is that MAOIs are still the treatment of choice for depression with atypical features, including in older patients. Although commonly assumed that SSRIs are equally effective, none of the second-generation antidepressants have been directly compared with MAOIs for this indication. To the contrary, trials have found SSRIs no better than TCAs for atypical depression.

Seeing patient after patient refuse nefazodone after learning (from me) about its black box warning, I address the problem of hepatotoxicity in “Nefazodone Revisited” (see page 184). It seemed odd to me that a 1 in 250,000 patient-year incidence of fulminant hepatic failure would deter all prospective users from taking an antidepressant that exacts no weight gain or sexual dysfunction. A visit to the US Census Bureau website (at www.census.gov/compendia/statab/cats/births_deaths_marriages_divorces.html) puts this figure in context. In 2007, the rate of fatalities by unintentional accidents (of which about one-third are motor vehicle accidents) ranged from 36.9 to 45 per 100,000 persons 15 to 75 years. (The rate of nonfatal, although serious, injuries from accidents is several-fold higher. By comparison, the rate of suicide in the US was 11.1 per 100,000 in 2007). I tell patients before I prescribe potentially toxic medications (virtually all over-the-counter and prescription drugs) that “You are more likely to die in a motor vehicle accident this year than develop [insert here].” Nonetheless, people view motor vehicle accidents and other unintentional injuries as only partly modifiable. The risk of needing a liver transplant, no matter how small, is entirely within their hands — by not taking the drug. This leads us to the field of risk communication, an area outside the scope of most medical school curricula. In this article, I review the literature on nefazodone and discuss the comparative risks associated with other psychotropics.

There are many more treatments that are underutilized, including somatic and psychological therapies for a broad range of psychiatric disorders. My hope in hosting this issue is that readers are inspired to consider assumptions about other relics of the past and investigate these, too.

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