

### Combining therapies

Dr. Henry A. Nasrallah is on target in his editorial, "Combination therapies are here to stay" (From the Editor, CURRENT PSYCHIATRY, May 2010, p. 11-12). Psychosis in the context of dementia is another area of interest. We have been thoroughly steeped in the "black-box" warning about antipsychotic use in dementia. The most common discussion point among psychiatrists in consideration of the managing complex dementia with psychotic disturbances is which medications to use and how to use antipsychotics when there is no other choice. The warning is certainly judicious; however, the fact is that almost every day this clinical situation could arise, placing us in a difficult position of weighing a complex risk vs safety analysis with no viable guidance and no real option other than to make decisions and involve family members in complicated informed consent discussions. Evidence also suggests that functional capacity in dementia may be enhanced by combining donepezil and memantine, which also is of consequence in dementia polypharmacy.

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### Propranolol for anxiety

How do the authors of "Do beta blockers cause depression?" (Medicine in Brief, CURRENT PSYCHIATRY, May 2010, p. 50-55) feel about using propranolol augmentation for patients with anxiety who are already taking a selective serotonin reuptake inhibitor and a benzodiazepine? I often prescribe propranolol because it has a different mechanism



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of action—but I am curious if others would consider doing more of this, provided the patient is at low risk for suicidal thoughts and attempts.

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### The authors respond

In 1966 Drs. Granville-Grossman and Turner published a seminal article on propranolol for anxiety disorders.<sup>1</sup> Their study included 16 patients who used propranolol, 20 mg/d, which had a beneficial effect on anxiety by alleviating autonomically mediated symptoms. This article also provided evidence for a belief that beta blockers are beneficial in anxiety mainly because they reduce somatic symptoms, a finding that has been supported by review articles.<sup>2,3</sup> We found only 2 studies examining adjunctive use of propranolol.<sup>4,5</sup> In these studies, propranolol combined with alprazolam was found to be well tolerated and effectively reduced somatic anxiety symptoms. Based on available evidence, the addition of a beta blocker could benefit patients who continue to experience

physical symptoms of anxiety despite being treated with psychotropics.

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### References

1. Granville-Grossman KL, Turner P. The effect of propranolol on anxiety. *Lancet*. 1966;1:788-790.
2. Hayes PE, Schulz SC. Beta-blockers in anxiety disorder. *J Affect Disord*. 1987;13:119-130.
3. Tyrer P. Anxiolytics not acting at the benzodiazepine receptor: beta blockers. *Prog Neuropsychopharmacol Biol Psychiatry*. 1992; 16:17-26.
4. Shehi M, Patterson WM. Treatment of panic attacks with alprazolam and propranolol. *Am J Psychiatry*. 1984;141(7):900-901.
5. Mendels J, Chernoff RW, Blatt M. Alprazolam as an adjunct to propranolol in anxious outpatients with stable angina pectoris. *J Clin Psychiatry*. 1986;47(1):8-11.

### Beta blockers, T3, and T4

Propranolol is used to treat thyroid storm specifically because of its action in blocking conversion of prohormone thyroxine (T4) to triiodothyronine (T3) ("Do beta blockers cause depression?" Medicine in Brief, CURRENT PSYCHIATRY, May 2010, p. 50-55). Because T3 is the basis of the basal metabolic rate, if T3 were decreased then the only other mechanism for energy is adrenaline. This would cause depression when adrenaline wasn't in use and anxiety when it was. This sounds like a direct link to depression and anxiety to me. The thyroid function test would show no change in thyroid-stimulating hormone, but an increase in T4 to compensate for the decrease in T3. There

continued on page 16

continued from page 8

are no medical standards to routinely look at T3 and the effect would not be seen anyway. I am not aware of research that explores this connection between beta blockers and depression.

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### Antidepressant complexity

I treat adults with bipolar II and cyclothymic disorders; I am concerned about the dogmatic view that antidepressants should not be used to treat bipolar spectrum disorders ("Antidepressants in bipolar disorder: 7 myths and realities," *CURRENT PSYCHIATRY*, May 2010, p. 40-49). As I have been advising my patients, managed care reviewers, and even a few psychiatric editors during the past several years, it is a flawed dogma for reasons identified by the author of this article, Dr. Joseph F. Goldberg. He correctly cites Tohen et al,<sup>1</sup> who showed a 56% response rate for fluoxetine plus olanzapine in treating bipolar depression vs olanzapine alone or placebo. He also cites another study by Amsterdam<sup>2</sup> on the efficacy of venlafaxine in bipolar II depression.

I would add 2 observations to Dr. Goldberg's critique. The frequently cited Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study by Sachs et al<sup>3</sup> argues antidepressants are not effective for bipolar depression.

What many colleagues may not know is that STEP-BD achieved only a 28% positive treatment response. Also, only 6% of subjects were taking atypical antipsychotics, usually high doses—typically olanzapine, >10 mg. These doses of olanzapine—like high doses of other mood stabilizers—may exacerbate fatigue and depressive symptoms. Secondly, the scant research and dogmatism about antidepressants in bipolar treatment has tended to focus on bipolar I disorder, as Dr. Goldberg points out. In addition, it tends to ignore the issue of highly prevalent comorbid anxiety disorders and attention-deficit/hyperactivity disorder in early-onset bipolar spectrum disorders.

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#### References

1. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60:1079-1088.
2. Amsterdam JD, Wang CH, Shwarz M, et al. Venlafaxine versus lithium monotherapy of rapid and non-rapid cycling patients with bipolar II major depressive disorder: a randomized, parallel group, open-label trial. *J Affect Disord*. 2009;112(1-3):219-230.
3. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007;356:1711-1722.

### Maximizing 'med checks'

I commend Dr. Douglas Mossman on his balanced perspective in "Navigating the 15-minute 'med check'" (*CURRENT PSYCHIATRY*, June 2010, p. 40-43).

Dr. Mossman was kind enough to cite my editorial<sup>1</sup> on the "prescriptive bond," in which I use the term "infamous" to describe the 15-minute med check. Indeed, there are instances when a brief encounter is inadequate to address the multitude of biologic, psychological, and social issues faced by a complex patient. However, I agree with Dr. Mossman that, for some patients, a well-managed 15-minute med check may be appropriate and useful. Much depends on how well the time is structured, as Dr. Mossman's article nicely describes. Indeed, some psychotic patients or those with extreme social phobic symptoms may not tolerate longer encounters. We must learn to do the best we can with the resources we have, while still advocating for greater access to appropriate mental health care for our patients.

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#### Reference

1. Pies RW. Psychiatrists, physicians, and the prescriptive bond. *Psychiatric Times*. April 16, 2010. Available at <http://www.psychiatrictimes.com/blog/couchincrisis/content/article/10168/1555057>. Accessed April 28, 2010.



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## Comparing medications for alcohol withdrawal

It is interesting to look at other agents that aide in treating alcohol withdrawal (AW) ("Alcohol withdrawal: When to choose an adjunctive anticonvulsant," *CURRENT PSYCHIATRY*, April 2010, p. 26-39). However, it would be more important to stress using chlordiazepoxide instead of lorazepam as long as there are no contraindications, because there is conclusive evidence that patients receiving chlordiazepoxide are hospitalized for fewer days. Presumably, there should be less morbidity and a smoother withdrawal likely related to chlordiazepoxide's longer half-life. What do the authors think about using chlordiazepoxide more often and what cutoff for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) would they suggest for not using chlordiazepoxide?

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### The authors respond

*Chlordiazepoxide and diazepam are time-honored choices for AW. Advantages include long half-lives, which allow for uniform blood levels across the day and reduce risk of withdrawal symptoms, including seizures, that may arise when blood levels drop. At the same time, this long half-life combined with the presence of active metabolites, dependence on Phase I metabolism, and higher lipophilicity could result in increased drug accumulation and redistribution into lipid storage*

*reservoirs, which could complicate the clinical picture. Alternatively, lorazepam, an intermediate-acting benzodiazepine that depends primarily on Phase 2 metabolism, is less affected by liver disease. Additional advantages of lorazepam are its lower lipophilicity compared with chlordiazepoxide and diazepam, and no active metabolites. For these pharmacokinetic benefits, in a group where liver dysfunction is presumed, lorazepam has grown in favor.<sup>2</sup>*

*Although there is a dearth of head-to-head efficacy comparisons between lorazepam and chlordiazepoxide/diazepam, a study of chlordiazepoxide and lorazepam in AW supported that during detoxification the longer-acting diazepam produced no withdrawal seizures; the lorazepam group had patients who developed seizures. However, when the initial lorazepam dosage was increased in a later study, patients' withdrawal was seizure-free. Efficacy was otherwise equal among treatment groups.<sup>1</sup>*

*The evidence seems to lead to an overall generalization that when dosed correctly, shorter- and longer-acting benzodiazepines (ie, lorazepam and chlordiazepoxide, respectively) are effective and safe, with the caveat that older patients and those with liver dysfunction should be treated with lorazepam.<sup>3</sup> However, is there a reliable and quick assessment of liver dysfunction in patients with alcohol use disorders?*

*Although the Child-Pugh classification score can be used, it typically is used to assess prognosis of chronic liver disease.<sup>4</sup> Using traditional serum biomarkers to predict hepatic dysfunction offers advantages and disadvantages. I offer the*

*following guidelines: gamma-glutamyl transpeptidase (GGTP)  $\geq 177$  U/L, AST  $\geq 63$  U/L, and ALT  $\geq 67$  U/L, statistically separates ( $P < .001$ ) heavy drinkers from moderate drinkers and abstainers; the former group is at greatest risk for alcoholic liver disease.<sup>5</sup> The majority of long-term heavy drinkers develop fatty liver disease, but only 10% to 35% develop hepatitis and 8% to 20% progress to cirrhosis.<sup>6</sup> Additionally, other limitations with using a priori serum biomarkers' range include the role of genetics, gender, race, and medical comorbidities<sup>7</sup> (ie, other causes of acute hepatitis, cholestasis, and liver congestion) in the development of alcoholic liver disease and their effect on these biomarkers.<sup>6</sup>*

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### References

1. Kumar CN, Andrade C, Murthy P. A randomized, double-blind comparison of lorazepam and chlordiazepoxide in patients with uncomplicated alcohol withdrawal. *J Stud Alcohol Drugs*. 2009; 70:467-474.
2. Bird RD, Makela EH. Alcohol withdrawal: what is the benzodiazepine of choice? *Ann Pharmacother*. 1994;28:67-71.
3. Hoey LL, Nahum A, Vance-Bryan K. A prospective evaluation of benzodiazepine guidelines in the management of patients hospitalized for alcohol withdrawal. *Pharmacotherapy*. 1994;14(5): 579-585.
4. Child-Pugh score. Available at: <http://www.doctorslounge.com/gastroenterology/scores/child.htm>. Accessed June 7, 2010.
5. Alatalo P, Koivisto H, Puukka K, et al. Biomarkers of liver status in heavy drinkers, moderate drinkers and abstainers. *Alcohol Alcohol*. 2009;44(2):199-203.
6. Gramenzi A, Caputo F, Biselli M, et al. Review article: alcoholic liver disease—pathophysiological aspects and risk factors. *Aliment Pharmacol Ther*. 2006;24(8):1151-1161.
7. Mueller S, Millonig G, Sarovska L, et al. Increased liver stiffness in alcoholic liver disease: differentiating fibrosis from steatohepatitis. *World J Gastroenterol*. 2010;16(8):966-972.