responses such as stress, anxiety, learning, and memory.[12] In 1993, the first ASO was applied in vivo in the brain and targeted the neuropeptide Y1 receptor mRNA.[13] The ASO inhibited neuropeptide Y1 receptor expression in rats and increased anxiety. This may represent a proof of concept that psychopathological features can be modulated by an ASO strategy. Brain-derived neurotrophic factor (BDNF) may pose another target, considering its pivotal role in neuroplasticity, network formation, and cognition.[14] An ASO that binds on *BDNF* natural antisense transcripts increased *BDNF* mRNA levels 2- to 7-fold along with neuronal outgrowth in vitro and in vivo.[15] Another target may be the dopamine receptor (DR). In 1993, an ASO targeting *DR2* mRNA successfully reduced striatal DR2 in rats.[16] Despite the encouraging progress in ASO strategies, the introduction of ASOs in psychiatry is lagging far behind to those investigated or even approved in neurological disorders. There are still many hurdles to overcome to improve diagnostics and treatment options. A first major challenge is to link molecular and cellular alterations to changes at the genome level. Second, molecular, cellular, and biochemical changes still have to be defined and associated with each disorder.[17] Although no safety concerns were identified for most of the currently available ASOs,[1,3] off-target effects may further limit the widespread ASO utilization, particularly in psychiatry. For example, a chronic overexpression of BDNF impaired learning and memory in mice.[18] However, there is no need for pessimism considering that the encouraging approaches as shown for SMA or AD were barely conceivable only a few years ago. As provided by ASOs, the perspective of efficient treatment could be a driving force in the inevitable necessary basic research in psychiatric disorders that may yield in introducing ASO strategies in this field in the future.

AUTHOR DISCLOSURE INFORMATION

Heiko Graf declares that he has no potential conflicts of interest or financial disclosures. Claudia Diana Wurster has received travel expenses for attending a meeting from Biogen, and she cooperates with Hoffmann-La Roche.

Heiko Graf, MD
Department of Psychiatry and Psychotherapy III
Ulm University
Ulm, Germany
heiko.graf@uni-ulm.de

Claudia Diana Wurster, MD
Department of Neurology
Ulm University
Ulm, Germany

REFERENCES

1. Schoch KM, Miller TM. Antisense oligonucleotides: translation from mouse models to human neurodegenerative diseases. *Neuron*. 2017;94:1056–1070.
2. Khorkova O, Wahlestedt C. Oligonucleotide therapies for disorders of the nervous system. *Nat Biotechnol*. 2017;35:249–263.
3. Wurster CD, Ludolph AC. Antisense oligonucleotides in neurological disorders. *Ther Adv Neurol Disord*. 2018;11:1–9.
4. Juliano RL. The delivery of therapeutic oligonucleotides. *Nucleic Acids Res*. 2016;44: 6518–6548.
5. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. 2017;377:1723–1732.
6. Scheltens P, Blennow K, Breteler MM, et al. Alzheimer's disease. *Lancet*. 2016;388:505–517.
7. O'Brien RJ, Wong PC. Amyloid precursor protein processing and Alzheimer's disease. *Annu Rev Neurosci*. 2011;34:185–204.
8. Kumar VB, Farr SA, Flood JF, et al. Site-directed antisense oligonucleotide decreases the expression of amyloid precursor protein and reverses deficits in learning and memory in aged SAMP8 mice. *Peptides*. 2000;21:1769–1775.
9. Hinrich AJ, Jodelka FM, Chang JL, et al. Therapeutic correction of ApoER2 splicing in Alzheimer's disease mice using antisense oligonucleotides. *EMBO Mol Med*. 2016;8:328–345.
10. Volloch V, Rits S. Results of beta secretase–inhibitor clinical trials support amyloid precursor protein-independent generation of beta amyloid in sporadic Alzheimer's disease. *Med Sci (Basel)*. 2018;6:1–13.
11. Smoller JW, Andreassen OA, Edenberg HJ, et al. Psychiatric genetics and the structure of psychopathology. *Mol Psychiatry*. 2018;9.
12. Eaton K, Sallee F, Sah R. Relevance of neuropeptide Y (NPY) in psychiatry. *Curr Top Med Chem*. 2007;7:1645–1659.
13. Wahlestedt C, Pich EM, Koob GF, et al. Modulation of anxiety and neuropeptide Y-Y1 receptors by antisense oligodeoxynucleotides. *Science*. 1993;259:528–531.
14. Castren E, Antila H. Neuronal plasticity and neurotrophic factors in drug responses. *Mol Psychiatry*. 2017;22:1085–1095.
15. Modarresi F, Faghihi MA, Lopez-Toleano MA, et al. Inhibition of natural antisense transcripts in vivo results in gene-specific transcriptional upregulation. *Nat Biotechnol*. 2012;30:453–459.
16. Zhang M, Creese I. Antisense oligodeoxynucleotide reduces brain dopamine D2 receptors: behavioral correlates. *Neurosci Lett*. 1993;161:223–226.
17. McCammon JM, Sive H. Challenges in understanding psychiatric disorders and developing therapeutics: a role for zebrafish. *Dis Model Mech*. 2015;8:647–656.
18. Cunha C, Angelucci A, D'Antoni A, et al. Brain-derived neurotrophic factor (BDNF) overexpression in the forebrain results in learning and memory impairments. *Neurobiol Dis*. 2009;33:358–368.

OPEN

Acetazolamide for Antipsychotic-Associated Weight Gain in Schizophrenia

To the Editors:

Acetazolamide is a sulfa-like moiety, a potent nonspecific inhibitor of carbonic anhydrase enzymes.[1] It came to medical use in 1952. It is a safe, effective, very economically priced, generic drug, which is in the World Health Organization list of essential drugs. Acetazolamide is available in oral and intravenous form.[2] Acetazolamide is indicated for centrencephalic epilepsies, idiopathic intracranial hypertension, secondary glaucoma, and preoperatively in acute angle closure glaucoma where delay of surgery is desired to lower intraocular pressure.[2] It appears to have beneficial effect in psychogenic polydipsia.[3] Common adverse effects of acetazolamide include tingling, palinopsia, dizziness, diuresis, tiredness, confusion, anorexia, and weight loss. One of the common adverse effects of the antipsychotic drugs is weight gain and metabolic adverse effects.[4]

Given the treatment compliance associated with weight gain and obesity, clinicians should monitor weight during the course of antipsychotic therapy and consider switching agents if excessive weight gain occurs.[5] Body weight and metabolic risk profile in patients receiving atypical antipsychotic medications need to be effectively managed with a weight control program including physical activity, which is difficult in illness such as schizophrenia.[6] Topiramate is an anticonvulsant that reportedly confers weight loss in patients receiving doses up to 300 mg/d.[7] Topiramate appears to inhibit specific carbonic anhydrase enzymes II and V compared with azetazolamide, which is a nonspecific inhibitor of carbonic anhydrase enzymes and has been demonstrated to decrease lipogenesis in adipose cells in vitro cell culture studies.[1]

Zonisamide, another antiepileptic drug, also a carbonic anhydrase inhibitor,[8] is known to cause weight loss in adolescents[9] and adults.[10]

Patients with idiopathic intracranial hypertension and mild visual loss assigned to either acetazolamide or placebo, all of whom received a 6-month telephone-based weight loss intervention, lost an average of 5.9% of initial body weight, consistent with the NHLBI (National Heart Lung and Blood Institute) guidelines of 5% to 10% of body

weight loss for clinically significant health benefit.[11] Ophthalmologists have concerns that acetazolamide retards weight gain when given to children. In a retrospective chart review, 22 well children with glaucoma taking oral acetazolamide for 3 months or more showed poor weight gain in a small subset of children.[12] Fifteen consecutive female patients with idiopathic intracranial hypertension associated with obesity were studied to determine the weight loss associated with resolution of papilloedema. Patients underwent weight loss on treatment with acetazolamide during the 24-week period. Weight loss of 3.3% ± 0.5% (mild) was observed among patients having a 1-grade change in papilloedema and 6.2% ± 0.6% was associated with a 3-grade (marked) change in papilloedema. Approximately 6% weight loss was associated with resolution of marked papilloedema in these patients.[13] A young obese lady gained significant weight after commencing risperidone and later developed headache and blurred vision. She was diagnosed to have benign intracranial hypertension due to risperidone usage. Withdrawing the offending drug and addition of acetazolamide 500 mg twice daily (given for benign intracranial hypertension) led to weight loss and drastically improved her symptoms within a month. Acetazolamide probably helped in recovery by diuresis.[14] A 49-year-old obese patient who was started on acetazolamide 250-mg twice daily had significant weight loss of 11.5 lb (5.21 kg) over 4 weeks similar to topiramate.[1]

In a study, when acetazolamide was given to 30 patients of which puberal periodic psychosis (6 cases), presenile atypical psychosis (7 cases), atypical psychosis (8 cases), atypical manic-depressive psychosis (2 cases), and atypical schizophrenia (7 cases), some extent of therapeutic effects of acetazolamide (500–1000 mg) as an antipsychotic was obtained in approximately 70% of the patients. High therapeutic effects were particularly observed in puberal periodic psychosis, presenile atypical psychosis, and atypical psychosis. Acetazolamide showed effectiveness in 10 of the 13 cases to which lithium carbonate and carbamazepine were ineffective. Acetazolamide was considered to have antipsychotic and prophylactic effects on atypical psychosis. Adverse effects were rarely observed in the study, and acetazolamide had a high safety margin.[15] Twenty-four chronic schizophrenia patients were treated successfully with the addition of acetazolamide plus thiamine to their unchanged existing therapies in a double-blind, placebo-controlled cross-over study. Therapeutic effects were measured by the scale for the assessment of positive symptoms and the scale for the assessment of negative symptoms. Overall 50% of the patients showed improvement on all the assessment scales.[16]

CONCLUSIONS

Several clinical studies have reported weight loss as an adverse effect of acetazolamide, and it has shown some beneficial effects in treating psychosis (hence no risk of increasing the primary illness). We conclude, based on the associated weight loss and the apparent improvement in psychotic symptoms, that randomized controlled clinical trials of acetazolamide in antipsychotic-related weight gain are indicated to confirm the associations.

ACKNOWLEDGMENT

We thank Professor Vishwajit L Nimgaonkar MD PhD, Professor of Psychiatry & Human Genetics, University of Pittsburgh and the Indian Association of Private Psychiatry (IAPP) for their support and encouragement.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

Anil Kakunje, DPM, MD
Department of Psychiatry
Yenepoya Medical College
Yenepoya University
Mangalore, India
anilpsychiatry@yahoo.co.in

Ashwini Prabhu, MSc, PhD
Sindhu Priya ES, M.Pharm
Yenepoya Research Centre
Yenepoya University
Mangalore, India

Ravichandra Karkal, MD
Rahyanath K. Pookoth, MSc
Department of Psychiatry
Yenepoya Medical College
Yenepoya University
Mangalore, India

Rekha PD, PhD
Yenepoya Research Centre
Yenepoya University
Mangalore, India

REFERENCES

1. Schneiderhan ME, Marvin R. Is acetazolamide similar to topiramate for reversal of antipsychotic induced weight gain? *Am J Ther*. 2007;14:581–584.
2. Parasrampuria J. Acetazolamide. In: Brittain HG, ed. *Analytical Profiles of Drug Substances and Excipients* vol. 22. Cambridge, MA: Elsevier; 1993:1–32.
3. Takagi S, Watanabe Y, Imaoka T, et al. Treatment of psychogenic polydipsia with acetazolamide: a report of 5 cases. *Clin Neuropharmacol*. 2011;34:5–7.
4. Maayan L, Correll CU. Management of antipsychotic-related weight gain. *Expert Rev Neurother*. 2010;10:1175–1200.
5. Ganguli R. Weight gain associated with antipsychotic drugs. *J Clin Psychiatry*. 1999;60:20–24.
6. Poulin MJ, Chaput JP, Simard V, et al. Management of antipsychotic-induced weight gain: prospective naturalistic study of the effectiveness of a supervised exercise programme. *Aust N Z J Psychiatry*. 2007;41: 980–989.
7. Krymchantowski A, Tavares C. Weight variations in patients receiving topiramate migraine prophylaxis in a tertiary care setting. *MedGenMed*. 2004;6:48.
8. Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. *Seizure*. 2004;13:S5–S9.
9. Nguyen ML, Pirzada MH, Shapiro MA. Zonisamide for weight loss in adolescents. *J Pediatr Pharmacol Ther*. 2013;18: 311–314.
10. Gadde KM, Kopping MF, Wagner HR, et al. Zonisamide for weight reduction in obese adults a 1-year randomized controlled trial. *Arch Intern Med*. 2012;172:1557–1564.
11. Weil R, Kovacs B, Miller N, et al. A 6-month telephone-based weight loss intervention in overweight and obese subjects with idiopathic intracranial hypertension. *Obes Sci Pract*. 2016; 2:95–103.
12. Sharan S, Dupuis A, Hébert D, et al. The effect of oral acetazolamide on weight gain in children. *Can J Ophthalmol*. 2010;45: 41–45.
13. Johnson LN, Krohel GB, Madsen RW, et al. Role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension. *Ophthalmology*. 1998;12: 2313–2317.
14. Ahmed H, Ali H. Risperidone induced weight gain leading to benign intracranial hypertension. *BMJ Case Rep*. 2011;2011: 10:1136.
15. Inoue H, Hazama H, Hamazoe K, et al. Antipsychotic and prophylactic effects of acetazolamide (Diamox) on atypical psychosis. *Folia Psychiatr Neurol Jpn*. 1984;38:425–436.
16. Sacks W, Esser AH, Feitel B, et al. Acetazolamide and thiamine: an ancillary therapy for chronic mental illness. *Psychiatry Res*. 1989;28:279–288.