PRACTITIONER FORUM

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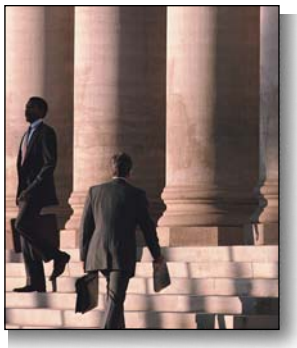

Tarvil for Tardive Dyskinesia: Are We Robbing Peter to Pay Paul?

When the glossy advertisement for Tarvil (SHS North America, Rockville, MD) crossed my desk in June 2003, it induced both a sense of excitement and a sense of dread. According to the manufacturer, Tarvil is a "medical food" intended to help reduce the symptoms of tardive dyskinesia (TD) in men with schizophrenia.[1]

On the one hand, the research is highly promising. A recent study showed that this product can reduce the symptoms of TD significantly—and even produce a complete remission—in male patients with schizophrenia.[2] How exciting if this new product were to be the answer psychiatrists have been searching for to allow patients to benefit from their antipsychotic medications without having to endure this common adverse effect.

But there is a catch. Because Tarvil is not calorie free, routine use without dietary modification is likely to induce weight gain—a problem patients with schizophrenia can ill afford. Antipsychotic medications already tend to cause patients to gain weight, and considering the compounding evidence of links between excessive weight, diabetes, and cardiovascular risks, the potential harm of additional weight gain is of concern.

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ROLE OF PHENYLALANINE IN TD

Tarvil was developed based on research over the past 20 years that has demonstrated a strong correlation between phenylalanine dysmetabolism and the development of TD in certain patients.[3–5] Studies also show that ingestion of a protein meal with a higher level of branched-chain amino acids (BCAAs) than of the aromatic amino acids (AAs) phenylalanine, tyrosine, and tryptophan (19.6% versus 7.5%) is correlated directly with a reduction in plasma AA concentrations.[3] The research is elegant in its straightforwardness, showing that BCAA treatment results in a reduction in phenylalanine levels that is associated significantly with decreases in TD symptoms.[2] Conversely, TD symptoms have been shown to be exacerbated in schizophrenic patients after phenylalanine ingestion.[6]

Tarvil is comprised of the BCAAs valine, isoleucine, and leucine, in a 3:3:4 ratio.[1] It's available in the form of a powder that is dissolved in water and taken orally three times a day: after breakfast, one hour before lunch, and one hour before dinner.[1]

Each 15-g packet of Tarvil contains 6.3 g of BCAAs.[1] Since the ideal dose of BCAAs is 222 mg/kg of body weight,[2] this usually works out to about three packets per day—or one packet per dose—for an average male patient.

TARVIL AND WEIGHT GAIN

Antipsychotic medications tend to promote both obesity and diabetes in patients with schizophrenia.[7] Moreover, schizophrenia itself may increase patients' risk of developing diabetes independently of the effects of antipsychotic medications.[8,9]

Research into the exact nature of the relationship between antipsychotics and glucose dysregulation continues, but the existence of this link hardly needs formal study—we see it before our very eyes. Prescribe olanzapine and watch your patient's weight soar within just a few short months. And while olanzapine is the undisputed heavyweight champion of antipsychotic-induced weight gain in schizophrenic patients[10–12]—with clozapine a close second[13]—the fact is that most antipsychotic medications tend to cause some degree of weight gain.[14]

Continued on page 53

Continued from page 48

Table. Artificial sweeteners approved or pending approval for use in the United States[16–21]

Name	Sweetness (x sugar)	FDA status	Notes
Acesulfame-K	200x	Approved since 1988	Noncaloric sweetener composed of carbon, nitrogen, oxygen, hydrogen, sulphur, and potassium atoms
Alitame	2,000x	Pending approval	Composed of L-aspartic acid and D-alanine, along with a novel amine
Aspartame	180x	Approved since 1981	Composed of phenylalanine and aspartate
Cyclamate	30–50x	Currently banned, but FDA considering a petition to reapprove	A sulfamic acid usually used as the sodium or calcium salt; first approved in 1949; FDA banned in 1970 based on evidence linking it to bladder cancer; subsequent studies failed to verify that link
Neotame	8,000x	Approved since 2002	Derivative of aspartame, but has no effect on phenylketonurics due to blockade of peptidases, thus reducing phenylalanine availability
Saccharin	300x	Approved (with mandatory warning label)	Derived from toluene; developed in 1879 and widely used since 1917; FDA considered limiting or banning use in 1970s based on research indicating link with bladder cancer in rats, but Congress passed moratorium on ban to allow further research; moratorium extended several times due to popular demand for product; FDA withdrew consideration of ban in 1991, but requires warning label on all products
Sucralose	600x	Approved since 1998	The only noncaloric sweetener made from sugar, through a process that selectively substitutes three atoms of chlorine for three hydroxyl groups on the sugar molecule

To help achieve its "pleasant pineapple flavor," Tarvil contains both sugar and the artificial sweetener acesulfame-K.[1] It's easy to see why the manufacturers chose acesulfame-K over the more widely used aspartame, which contains phenylalanine and aspartic acid. Since the goal of Tarvil is to reduce plasma levels of phenylalanine significantly, aspartame is not the way to sweeten the pot.

But though acesulfame-K is a noncaloric sweetener, the presence of sugar in Tarvil adds calories: 52 in each 15-g packet.[1] If a patient takes one packet three times a day, the effect would be an additional 156 calories above the 1,800 to 2,000 recommended daily for the average male adult—an 8% to 9% increase.

Continued on page 56

Continued from page 53

Since 3,500 stored calories represent a net gain of 1 lb of body fat,[15] patients taking three packets of Tarvil per day will gain 1 lb approximately every three weeks and 17 lb each year—in addition to any weight gain related to antipsychotic medications. Although it's possible that ingesting Tarvil before a meal might suppress the appetite, resulting in consumption of fewer calories during the meal, it's reasonable to assume that, for most patients, the overall daily caloric intake would be increased.

THE SWEETENER CONUNDRUM

But Tarvil is only part of the problem. Although the manufacturers of this product have avoided using the phenylalanine containing aspartame in order to preserve the anti-TD effects of BCAAs, patients still have plenty of opportunities to ingest aspartame—perhaps without even realizing it. Aspartame is everywhere. Just stroll down the aisle of any supermarket and examine the ingredients of items labeled "diet": diet soft drinks, coffee, sugar free gelatin, light ice cream, sugar free hard candy. It's hard to find a "diet" product these days that uses anything else! Although there are several other artificial sweeteners on the market and awaiting FDA approval (Table),[16–21] aspartame is used in over 6,000 foods and beverages worldwide.[22]

So if we give our patients Tarvil to reduce their vulnerability to TD, shouldn't we also instruct them to avoid diet products containing aspartame? And if we do that, we need to take a look at the impact a potential compensatory increase in sugar would have on patients' weight and blood glucose levels.[23]

By simply replacing diet soft drinks containing aspartame with regular soft drinks containing sugar, for example, a patient would take in an additional 160 calories per can. Three cans of regular soda daily would add 480 calories per day, which represents a gain of 1 lb per week, or over 50 lb per year. Add to this the 17 lb per year that Tarvil use could add, and it becomes apparent that a male patient with schizophrenia who takes Tarvil as directed and replaces diet soft drinks with regular soft drinks, without initiating a formal diet and exercise regimen, could gain upwards of 70 lb per year. And this is in addition to the adipose-generating effects of his psychotropic medication.

PATIENT EDUCATION IS KEY

Tarvil is a wonderful product that has the potential to reduce one of the most significant adverse effects of antipsychotic medications and help patients with schizophrenia improve their quality of life. But how much good are we truly doing for our patients if we simply replace the risk of TD with an increased risk of weight gain, diabetes, and cardiovascular disease?

We all recognize how difficult it is to motivate ourselves to begin and maintain a consistent diet and exercise regimen. We can't expect our patients who are already dealing with schizophrenia to have more willpower than individuals without serious mental illness. We must find other ways to help our patients stay physically fit and metabolically healthy without adding to their emotional burden.

In recognition of this, the psychiatric establishment should be at the forefront of a movement to educate patients about the importance of choosing nutritional supplements wisely and the potential risks that food products may carry. At the same time, diet product manufacturers should be encouraged to take advantage of the wide selection of artificial sweeteners available in order to provide consumers with a variety of diet options—including many that do not rely on sweeteners containing phenylalanine. Until we do, encouraging patients to consume Tarvil may simply be trading one risk for another. ●

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Continued on page 62

Continued from page 56

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